Chronisch Vermoeidheidssyndroom: diagnose, behandeling en zorgorganisatie

KCE reports 88A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2008

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Titel:	Chronisch Vermoeidheidssyndroom: diagnose, behandeling en zorgorganisatie.
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Externe experten:	De volgende 20 experten verleenden, in het kader van de samenwerking met de Hoge Gezondheidsraad, advies voor dit rapport: Joel Boydens (Christelijke Mutualiteit, Psychiater); Elie Cogan (ULB, Hôpital Universitaire Erasme, service de Médecine Interne); Els Coremans (UCL, Cliniques Universitaires site de Mont-Godinne, service de Psychiatrie); Tom Declercq (UGent, departement Geneeskunde vakgroep Huisartsgeneeskunde en Eerstelijnsgezondheidszorg); Koen Deraedt (RIZIV, Directie verzorgingsinstellingen en -diensten); Benjamin Fischler (Voorzitter werkgroep CVS Hoge Gezondheidsraad; consulent Psychiatrie Sint Pieterziekenhuis Brussel); Michel Lambert (UCL, Cliniques Universitaires St Luc, service de Médecine Interne); Patrick Luyten (KULeuven, departement Psychologie); Etienne Masquelier (UCL, Cliniques Universitaires St Luc, service de Médecine Physique et Réadaptation); Didier Macquet (CHU Liège, service de Physiothérapie); Greta Moorkens (UA, UZ Antwerpen, dienst Inwendige Geneeskunde); Eddy Neerinckx (KULeuven, departement Bewegings- en revalidatiewetenschappen); Jo Nijs (VUB, departement Lichamelijke opvoeding en kinesitherapie; Hogeschool Antwerpen departement Gezondheidszorg); Carine Poppe (UGent, departement Psychologie); Daniel Spooren (UGent, departement Psychologie); Boudewijn Van Houdenhove (KUL-UZLeuven, dienst Psychiatrie); Peter Van Wambeke (KUL-UZLeuven, dienst Fysische geneeskunde en revalidatie); Brigitte Velkeniers (VUB- UZBrussel, dienst Inwendige Geneeskunde); Elke Van Hoof (VUB, departement Psychologische en Educatieve Wetenschappen; Universiteit Hasselt, departement Geneeskunde); Dirk Vogelaers (UGent-UZ Gent, dienst Inwendige Ziekten)
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Conflict of interest:	De volgende 7 experten zijn werkzaam in een referentiecentrum voor CVS: Els Coremans, Greta Moorkens, Carine Poppe, Daniel Spooren, Boudewijn Van Houdenhove, Peter Van Wambeke, Dirk Vogelaers. De volgende 2 experten waren in het verleden werkzaam in een referentiecentrum voor CVS: Michel Lambert, Etienne Masquelier.
Disclaimer:	De externe experten hebben aan het wetenschappelijke rapport meegewerkt dat daarna aan de validatoren werd voorgelegd. De validatie van het rapport volgt uit een consensus of een meerderheidsstem tussen de validatoren. Alleen het KCE is verantwoordelijk voor de eventuele resterende vergissingen of onvolledigheden alsook voor de aanbevelingen aan de overheid.

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VOORWOORD

In 2002 richtte de Belgische Overheid referentiecentra voor het Chronisch Vermoeidheidssyndroom op, en ze was daarmee één van de koplopers in Europa. Bovendien werden de resultaten van de behandelde patiënten door de centra zelf systematisch geregistreerd, een primeur in de Belgische revalidatiewereld. Uit een eerder evaluatierapport bleek dat de resultaten na maanden tot een jaar behandeling gemiddeld eerder beperkt waren: de klachten van moeheid en het psychisch functioneren van de behandelde volwassenen verbeterden, maar er was geen duidelijk effect op vlak van inspanningscapaciteit, kwaliteit van leven en hernemen van arbeid. De ondersteuning vanuit de referentiecentra naar eerste en tweedelijnszorg voor deze patiëntengroep, kwam ook maar moeizaam op gang.

Binnenkort vervalt de financieringsovereenkomst van het RIZIV met de referentiecentra. De vraag rijst nu hoe het verder moet gaan: bieden deze centra de best haalbare en meest aangewezen zorg? Of zijn er andere manieren die betere en meer doelmatige resultaten zouden kunnen geven? Wat is wetenschappelijk de beste medische praktijk voor de aanpak van CVS? Deze vraag stelde het RIZIV aan de Hoge Gezondheidsraad met tegelijkertijd de vraag aan het KCE om de huidige wetenschappelijke stand van zaken op een systematische manier op een rijtje te zetten. Het is niet de eerste keer dat het KCE de eer te beurt valt om de Hoge Gezondheidsraad wetenschappelijk te mogen ondersteunen. Opnieuw bleek het een vruchtbare samenwerking waarbij diverse experts van de werkgroep van de Hoge Gezondheidsraad hun beste beentje hebben voorgezet, waarvoor onze welgemeende dank. Dit rapport dient dan ook gelezen te worden samen met de aanbevelingen van de Hoge Gezondheidsraad.

We hopen dat dit rapport ertoe kan bijdragen om op een objectieve manier te beschrijven wat we anno 2008 over CVS weten en misschien nog meer wat we niet weten en waar dringend meer klinisch onderzoek van hoge kwaliteit nodig is.

Gert Peeters
Adjunct Algemeen Directeur a.i.

Jean Pierre Closon
Algemeen Directeur a.i.

Samenvatting

DOELSTELLING

In 2002 erkende het RIZIV, op verzoek van de overheid, 4 Referentiecentra voor volwassenen en een Referentiecentrum voor kinderen, die lijden aan CVS. In 2006 evalueerde een beschrijvend rapport deze Referentiecentra (RC's). De financieringsovereenkomst met de RC's vervalt op 30 september 2008 en het RIZIV moet nu beslissen over de toekomstige financiering van de zorgverstrekking aan CVS patiënten. Het RIZIV vroeg aan het KCE om een wetenschappelijke basis te leveren voor de toekomstige patiëntenzorg, terwijl aan de Hoge Gezondheidsraad werd gevraagd op basis hiervan aanbevelingen te formuleren.

De voornaamste doelstellingen van deze studie zijn het actualiseren van de evidence-based kennis over diagnose, behandeling, economische gegevens en patiëntenkwesties van CVS; en het zoeken naar alternatieve organisatorische modaliteiten voor de verzorging van CVS patiënten in andere landen.

METHODOLOGIE

Op basis van de EBM methodologie werd een literatuuroverzicht gemaakt over definitie, behandeling, economische gegevens en patiëntenkwesties van CVS. Daarna werd in de wetenschappelijke en grijze literatuur gezocht naar een zorgorganisatiemodel voor chronische aandoeningen. Informatie over de verzorging van CVS in 5 geselecteerde westerse landen werd ingezameld aan de hand van een vragenlijst die aan contactpersonen werd gezonden. Er wordt een overzicht gegeven van de Belgische CVS gegevens, waaronder het RIZIV rapport (2006) over de Referentiecentra, en aanvullende cijfers van het RIZIV voor de jaren die nog niet in het rapport opgenomen waren. Tenslotte worden conclusies getrokken uit het voorgaande en wordt op basis hiervan de verzorging van CVS in België geëvalueerd.

RESULTATEN

DEFINITIE VAN CVS

Er bestaan verschillende definities van CVS[a], maar geen enkele daarvan heeft bewezen meer waard te zijn dan een andere, en alle werden ze geformuleerd door experts. De twee meest gebruikte definities van CFS zijn die van het International Centres for Disease Control (CDC) 1994 (gekend onder de naam "definitie van Fukuda") en de Britse definitie, voorgesteld in 1991 (Oxford). De CDC 1994 definitie is gebaseerd op een internationale consensus van onderzoekers en wordt op dit moment gebruikt in de Belgische CVS Referentiecentra (RC's). NICE (National Institute for Clinical Excellence, UK) deed in 2007 een voorstel voor aanpassing van de diagnostische criteria, deels op basis van expert consensus.

Een essentieel criterium voor de diagnose van CVS is in alle definities het optreden van invaliderende vermoeidheid gedurende 6 maanden. NICE stelt voor om de diagnose reeds na 4 maanden moeheid te bevestigen, maar dit dient nog verder internationaal en wetenschappelijk gevalideerd te worden. Wat betreft behandeling, zijn veel praktiserende zorgverstrekkers op gebied van CVS van oordeel dat het voor de patiënten veel beter zou zijn als ze vroeger zouden worden doorverwezen voor behandeling, in plaats van te wachten tot de symptomen gedurende zes maanden aanwezig zijn. Dit steunt echter ook niet op wetenschappelijke gegevens.

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a In dit rapport wordt de term "Chronisch Vermoeidheidssyndroom" gebruikt overeenkomstig de wetenschappelijke definities die een duidelijk onderscheid maken tussen CVS en Fibromyalgie. In België echter, worden de termen CVS en Fibromyalgie soms door elkaar gebruikt in het dagelijks taalgebruik, dit is echter niet het geval in dit rapport.

Door de NICE Guideline Development Group werd een ernstgradatie opgesteld die een onderscheid maakt tussen milde (personen zijn mobiel, kunnen voor zichzelf zorgen en kunnen met wat moeite, lichte huishoudelijke taken verrichten), matige (personen hebben een verminderde mobiliteit en zijn beperkt in alle dagelijkse activiteiten) en ernstige CVS patiënten (personen kunnen slechts een minimum aan dagelijkse taken verrichten of ze zijn totaal niet mobiel en kunnen die taken niet zelf doen, ze liggen meestal in bed). Wetenschappelijke studies trachten een ernstgradatie op te stellen aan de hand van gestandaardiseerde vragenlijsten, maar het nut en de validiteit van dit classificatiesysteem dienen nog verder uitgewerkt te worden.

Omdat in de literatuur geen eenduidig etiologisch concept of definitief patho-fysiologisch proces als oorzaak voor CVS werd beschreven, lijkt het *biopsychosociale* model aan patiënten en therapeuten de meest coherente benadering te bieden voor het begrijpen van het probleem en het starten van een behandeling. Dit model suggereert dat zodra een ziekte tot uitdrukking komt, ze wordt beïnvloed door het gedrag en de wijze waarop de patiënt zich aanpast, terwijl de fysiologische en psychologische effecten die hieruit voortvloeien op hun beurt het ziekteproces wijzigen of in stand houden. De combinatie van elk van deze componenten is verschillend voor elke patiënt. Er is meer onderzoek nodig naar de verschillende gebieden van dit model, zowel biologisch als psychosociaal, om het probleem CVS ten volle te begrijpen en zo het pad te effenen naar nieuwe behandelingsmogelijkheden.

BELGISCHE CVS REFERENTIECENTRA VOOR VOLWASSENEN

Diagnose

Het huidige bewijsmateriaal legt er de nadruk op dat de diagnose van CVS alleen kan worden gesteld op basis van klinische symptomen. Zonder alarmsignalen die op andere aandoeningen wijzen, moeten andere medische aandoeningen worden uitgesloten. Dit dient louter op basis van bloed- en urineanalyses te gebeuren, waarbij sommige testen wel en andere niet dienen uitgevoerd te worden. Het loont de moeite om de Belgische Richtlijnen die worden voorgesteld door de Hoge Gezondheidsraad, te actualiseren in overeenstemming met de huidige literatuurgegevens. Vooraleer naast deze basisonderzoeken, ook nog andere evaluaties routinematig worden aangeboden, moeten wetenschappelijke onderzoeken eerst hun impact op de diagnose en op de hieruit voortvloeiende verzorging voor deze groep patiënten, bevestigen.

Tot op heden is de invloed van de medische zorgniveaus (primair, secundair, tertiair) op gebied van nauwkeurigheid en doeltreffendheid van de diagnosticering van CVS nog niet wetenschappelijke onderzocht.

Volgens de NICE richtlijnen kan de diagnose worden gesteld door huisartsen. Het feit dat in Belgische RC's bij ca. 90% van de doorverwezen patiënten de veronderstelde diagnose van CVS ook kon worden bevestigd, lijkt hieraan te beantwoorden; de oorzaken voor dit hoge percentage werden tot op heden nog niet onderzocht. In sommige CVS centra in het buitenland lag het aantal bevestigde gevallen van CVS diagnose veel lager. Ook nam de diagnostische fase in de RC's veel tijd in beslag (4-5 maanden), en stegen de laatste jaren de kosten voor diagnostische evaluaties meer dan voor revalidatie, wat niet in overeenstemming is met de NICE richtlijnen. Volgens NICE kunnen de initiële onderzoeken bij personen die op het spreekuur komen met klachten van vermoeidheid door hun huisarts worden uitgevoerd, maar alle ernstige gevallen moeten voor advies onmiddellijk doorverwezen worden naar een CVS specialist. Bij milde en matig ernstige gevallen kan de huisarts starten met de algemene strategie en behandeling maar zou in geval van milde aantasting een verwijzing naar speciale CVS diensten met de patiënt moeten worden besproken binnen de 6 maanden na de eerste raadpleging; voor patiënten met matige klachten zou dit binnen de 3-4 maanden moeten gebeuren.

Behandeling van CVS bij volwassenen

Er werd geen specifiek zorgorganisatiemodel voor CVS in de literatuur aangetroffen.

Van de zorgmodellen die voor andere chronische aandoeningen bestaan (bijvoorbeeld diabetes, COPD/Chronisch Obstructief Longlijden), werd het "Chronisch Zorgmodel" (Chronic Care Model of CCM) (Wagner, 2001) in verschillende landen gebruikt om wijzigingen te introduceren of te onderzoeken bij de verzorging van chronische aandoeningen. Het Chronic Care Model bestaat uit zes pijlers, namelijk 1) 'lokale ondersteuning' 2) 'organisatie van de zorginstelling' 3)'organisatie van de zorgverlening' 4) 'stimuleren van zelfzorg' 5) 'werken volgens medische richtlijnen' en 6) 'informatiesystemen'. De nadruk ligt op uitgebreide zorg met een sterke betrokkenheid van de lokale zorginstellingen, geïntegreerde zorg en zorgcoördinatie, gezamenlijke doelstelling tussen patiënt en zorgverlener, de promotie van gezondheidseducatie en zelfzorg, een pleidooi voor het gebruik van evidence-based richtlijnen en het gebruik van informatietechnologie om de zorgorganisatie te ondersteunen. Er zijn zwakke aanwijzingen dat het introduceren van ten minste één element uit het CCM de zorg voor chronische patiënten zou kunnen verbeteren.

Volgens NICE, en in overeenstemming met het Chronic Care Model, zouden alle gezondheidsverstrekkers moeten trachten een ondersteunende en samenwerkende rol te spelen in de relatie met de CVS patiënt en zijn/haar familie en verzorgers. Tijdens alle zorgfasen moet gedeelde besluitvorming en een patiëntgerichte behandeling plaatsvinden. Het benadrukken van deze aspecten in de zorg voor CVS patiënten, kan er voor zorgen dat zij meer het gevoel krijgen dat hun klachten door professionele zorgverstrekkers ernstig worden genomen.

Spontaan herstel van CVS vindt meest plaats binnen de eerste 5 jaar van de ziekte, maar dit is maar een laag percentage patiënten (gemiddeld percentage van 7%) terwijl het aantal patiënten waarvan de toestand verbetert hoger ligt (gemiddeld percentage van 39,5%) en toeneemt in de loop van de tijd (na 5 en 10 jaar). Zonder interventie verergeren de symptomen in 5-20% van de gevallen.

Een belangrijk punt waar door NICE de nadruk op wordt gelegd is dat men niet mag wachten met de behandeling van de symptomen tot de definitieve diagnose is gesteld. Er wordt immers vermoed dat hoe sneller de patiënt wordt behandeld, hoe groter de kans is dat hij terug een normaal leven zal kunnen leiden.

Farmacologische behandelingen

Op dit moment zijn er geen aanwijzingen voor een gekende farmacologische behandeling of geneeswijze voor CVS. Behandeling van de symptomen moet gebeuren zoals in de gebruikelijke klinische praktijk. Aanbevelingen worden gedaan.

Revalidatie

Op dit moment heeft nog geen enkele behandeling aangetoond dat ze "genezing" brengt voor alle gevallen van CVS. De enige behandelingsstrategieën waarvan duidelijk bewezen is dat ze voordelen bieden, zijn de Cognitieve Gedragstherapie (CGT) en de Graduele Oefentherapie (Graded Exercise Therapy/GET). CGT maakt gebruik van geplande actieve en rustperioden, een geleidelijke toename van activiteiten, het opbouwen van een slaaproutine en cognitieve herstructurering van irreële gedachten en veronderstellingen, samen met de patiënt. GET gebruikt een gestructureerd activiteiten management programma dat een geleidelijke toename van lichamelijke activiteiten nastreeft (bijvoorbeeld wandelen), eveneens in samenwerking met de patiënt. Sommige patiënten geven de voorkeur aan pacing wat gebaseerd is op het principe van evenwicht tussen activiteit en rust; dit wordt momenteel geëvalueerd in een groot onderzoek (PACING studie).

Een sterk punt van de Belgische RC's is het routinematige gebruik van deze evidence-based therapieën. Al bij al kunnen de bekomen resultaten als teleurstellend beschouwd worden.

De reden hiervoor is niet duidelijk; verschillende factoren kunnen een rol gespeeld hebben. Opvallend is ook het verschil tussen de 3 Nederlandstalige centra en het Franstalige centrum. Terwijl de Nederlandstalige centra snel hun toegekende capaciteit bereikten, bereikte het Franstalige centrum hoogstens 50% van zijn capaciteit. De reden hiervoor is niet duidelijk, en werd in dit rapport ook niet bestudeerd.

Verschillende aspecten van de zorgverstrekking in de Belgische RC's moeten nog verder geëvalueerd worden in goed opgezette studies. Bewijs voor de doeltreffendheid van groepstherapie (vergeleken met individuele therapie), evenals voor de combinatie van CGT en GET is tot nu toe beperkt gebleven. Ook heeft geen enkel onderzoek zich tot nu toe bezig gehouden met het aantal therapiesessies dat nodig is om een verbetering te bekomen. In de Belgische RC's is dit gemiddeld 41 tot 62 uur per patiënt, en dit is meer dan beschreven wordt in klinische onderzoeken (gevoerd in de UK en Nederland), in de literatuur (meestal 10-16 uur) en in een van de andere bestudeerde landen (Noorwegen).

Er bestaat een consensus in de literatuur, die trouwens ook wordt gedeeld door NICE, dat wanneer CGT en GET worden gegeven aan CVS patiënten, deze therapieën zouden moeten worden aangepast aan deze specifieke aandoening. In de NICE richtlijnen wordt een algemeen advies gegeven over de inhoud van de therapie, evenals over aspecten van de therapieën die kunnen worden aangeboden wanneer CGT of GET niet mogelijk zijn. In de literatuur treffen we verschillende voorbeelden van therapeutische handleidingen aan die hun waarde hebben bewezen in wetenschappelijke onderzoeken over dit onderwerp. In de Belgische RC's gebruikt elk centrum zijn eigen therapeutische handleiding.

Recent bewijsmateriaal (1 RCT en 1 studie van lagere kwaliteit) duidt er op dat er minder kans is op gunstig resultaat als CGT of GET worden gegeven door minder gekwalificeerde of onervaren therapeuten. Dit wordt ook erkend door NICE. Het is niet duidelijk volgens welk protocol de professionele zorgverstrekkers die de dagelijkse therapie verzorgen in de Belgische RC's opgeleid zijn.

Slechts één prospectieve RCT rapporteerde over kosteneffectiviteit; daarbij werd CGT vergeleken met niet-behandeling. Over een follow-up periode van 14 maanden was de winst die werd geboekt door CGT vergeleken met niet-behandeling inzake kwaliteit van leven slechts gering en statistisch onzeker. Hoewel CGT de directe medische en niet-medische kosten leek te doen dalen, bleef de totale directe kost voor CGT hoger dan voor niet-behandeling. CGT werd kostenbesparend (in de context van Nederland) wanneer ook de indirecte kosten in rekening werden gebracht, d.w.z. wanneer de dagen dat de patiënten niet in staat waren te werken door hun aandoening in de berekeningen werden opgenomen; deze conclusie bleef echter ook onzeker. Er zijn meer onderzoeken nodig vooraleer een duidelijke conclusie over de kosteneffectiviteit van CGT mogelijk is.

Educatieve sessies voor familie

Geen enkele studie van hoge kwaliteit evalueerde het effect van educatieve sessies voor familie, maar volgens het biopsychosociale model, en in overeenstemming met het Chronic Care Model, zou dit een van de elementen kunnen zijn die bijdraagt tot de algemene impact van patiëntzorg voor CVS. Alle Belgische CVS centra begonnen met educatieve sessies voor familie als onderdeel van hun algemeen therapieaanbod.

Werkhervatting

Patiënten die gedurende vele jaren ziek waren en lange perioden van afwezigheid wegens ziekte hadden, hebben het moeilijker om het werk te hervatten. Er werd geen primair onderzoek aangetroffen betreffende de beste manier om werkherneming aan te pakken, maar door de NHS en de Nederlandse Nationale Gezondheidsraad werden adviezen gegeven aan werkgevers en CVS patiënten die hun werk wilden hernemen.

Zorgorganisatie

Geïntegreerde Zorgverstrekking

Volgens het Chronic Care Model, en volgens de NICE richtlijnen voor CVS, zou de zorgverstrekking moeten plaatsvinden op een geïntegreerde en gecoördineerde manier tussen de verschillende zorgniveaus. Dit was ook een duidelijke taak die door de Belgische regering en het RIZIV werd afgebakend toen de Referentiecentra werden opgericht in 2002, en specifieke financieringsmodaliteiten ter beschikking werden gesteld.

Tot dusver werd dit doel niet bereikt door de RC's. Bijvoorbeeld, hoewel de verwijzende arts telefonisch of per brief op de hoogte werd gehouden, werden er maar weinig andere initiatieven genomen om tussen de eerstelijns en tweedelijns zorgverstrekking en de referentiecentra tot een gezamenlijke zorg voor de patiënt te komen. Het voornaamste doel van het project, nl. een systeem in drie niveaus te ontwikkelen waarbij veel of zelfs de meeste patiënten in eerstelijn of tweedelijn zouden worden behandeld en zo dicht mogelijk bij hun woonplaats, werd niet bereikt. Het is duidelijk dat andere wegen zullen moeten worden bewandeld om dit doel te bereiken. Anderzijds zijn er maar weinig kwaliteitsvolle studies over de doeltreffendheid van de zorgverstrekking aan CVS patiënten in eerstelijns- of niet-gespecialiseerde tweedelijnszorg. Internationaal werd dit model geïmplementeerd in Engeland waar de coördinerende centra (CNCC's) en/of lokale multidisciplinaire teams (LMDT's) therapie kunnen aanbieden maar ook de behandelingsplannen bespreken met lokale zorgverstrekkers en zorgen voor hulpverlening en opleiding waar nodig. Uitkomsten worden geregistreerd op een uniforme en systematische manier, maar er zijn nog geen resultaten beschikbaar. Aangezien er nog geen aanwijzingen voor de doeltreffendheid van dit model beschikbaar zijn, is voorzichtigheid geboden met het introduceren van een gelijkaardig model in België en moeten de resultaten wetenschappelijk geëvalueerd worden.

Ernstig zieke personen

In Engeland zorgen veel LMDT's voor één of andere vorm van thuiszorg voor deze groep patiënten die niet naar gespecialiseerde ziekenhuizen kunnen komen. In België is dit nog niet het geval. Een grote studie wordt momenteel uitgevoerd waarin de behandeling door verpleegsters bij de patiënten thuis wordt geëvalueerd (FINE studie).

Aanvulling door het College van de Hoge Gezondheidsraad (HGR-CSS)

Idealiter kadert een samenwerkingsverband tussen de verschillende zorgniveau's voor CVS-patiënten in een breder systeem van getrapte zorgorganisatie voor andere chronische aandoeningen met een bio-psycho-sociale achtergrond. Knelpunten in het opstellen van een dergelijk systeem werden reeds vroeger omschreven (Advies Hoge Gezondheidsraad nr. 7814 dd. 13/4/2005). Moeilijkheden zijn het tot stand brengen van communicatie en multidisciplinair overleg, het voorzien van basisopleiding en voortgezette vorming, en het voorzien van gepaste vergoedingen voor de betrokken medewerkers.

BELGISCH CVS REFERENTIECENTRUM VOOR KINDEREN

Gegevens over kinderen en adolescenten zijn nog beperkt; het Belgische Referentiecentrum (RC) voor kinderen heeft tot dusver maar beperkt ervaring met deze groep.

Het Belgische RC werkt op een geïntegreerde manier, en biedt advies en ondersteuning in de huiselijke omgeving van het kind. Adolescenten worden soms ook residentieel verzorgd in het "Zeepreventorium" (De Haan).

Volgens NICE, moet de diagnose gebaseerd worden op de 1994 CDC criteria. NICE stelt ook voor om de diagnose bij kinderen te stellen na 3 maanden onverklaarde moeheid, maar deze aanbeveling is enkel gebaseerd op expert consensus. Na 6 weken vermoeidheid wordt aangeraden om door te verwijzen naar een kinderarts die belast is met de definitieve diagnose. De prognose is meestal beter bij jongeren dan bij volwassenen, gedeeltelijk of volledig herstel kan worden verkregen na 3-4 jaar.

Er werd aangetoond dat CGT voor verbetering kan zorgen bij adolescenten, maar het is nodig om meer onderzoek te doen naar dit aspect. In de informatie die werd gevonden voor de geselecteerde landen wordt therapie voor kinderen meestal individueel gegeven.

Meer onderzoek is nodig vooraleer een definitief advies te geven over de zorg voor kinderen en adolescenten met CVS.

AANBEVELINGEN

Tot hiertoe was het niet mogelijk om vanuit de ervaring van de CVS -referentiecentra gefundeerde wetenschappelijke richtlijnen op te stellen voor diagnose en behandeling van verwezen patiënten. Bovendien hebben deze centra hun belangrijkste missie niet vervuld, namelijk het ontwikkelen van een getrapte zorgorganisatie waarin zij de eerste lijn zouden ondersteunen.

Rekening houdend met deze vaststellingen, beveelt het KCE aan om de financiering van de referentiecentra niet verder te zetten tenzij onder veel striktere voorwaarden.

Concreet:

1. Het is aan te bevelen dat een meer gestructureerde zorgorganisatie ingevoerd wordt voor CVS in België, waarbij de eerste lijn (huisarts, kinesitherapeut, psycholoog…) een centrale rol dient te krijgen, in samenwerking met nabijgelegen 2de lijncentra en een referentiecentrum. Een herverdeling van de financiële middelen voor de conventie dient dit samenwerkingsverband te weerspiegelen. Een deel van deze middelen zou ook kunnen gaan naar kinesitherapeuten en naar psychotherapeuten (privé of in centra voor Geestelijke Gezondheidszorg). Daarbij dienen aan deze zorgverstrekkers voorwaarden gesteld te worden aangaande vorming, het gebruik van handleidingen en de integratie binnen de toekomstige zorgnetwerken. Het uitbouwen van een dergelijke gestructureerde zorgorganisatie dient in een eerste fase te gebeuren onder de vorm van een experiment.
2. Bij het opstarten van dit getrapte samenwerkingsverband (in de eerste fase onder experimentele voorwaarden) dient een wetenschappelijke werkwijze in acht genomen te worden (EBM en gezondheidseconomie). Dit is belangrijk om er zeker van te zijn dat op termijn valide gegevens beschikbaar zullen zijn die de nieuwe aanpak vergelijken met de vorige zowel voor de patiënt (effectiviteit) als voor de gemeenschap (kosteneffectiviteit). Bij het opstarten van een nieuwe conventie zou een gedeelte van de financiering kunnen voorzien worden voor deze evaluatie.
3. Er zijn empirische gegevens die erop kunnen wijzen dat vroegtijdige begeleiding van CVS meer kans biedt op een normaal leven en goede maatschappelijke reïntegratie. Om deze reden zou elke patiënt begeleid moeten worden vanaf het ogenblik dat de diagnose van CVS vermoed wordt. Het resultaat van een vroegtijdige begeleiding dient wetenschappelijk geëvalueerd te worden, en vergeleken te worden met de beschikbare literatuurgegevens.
4. Gezien er nog onvoldoende studies uitgevoerd werden die het effect van groepstherapie bestuderen, en gezien anderzijds het effect van individuele therapie (CGT of GET) wel aangetoond is, zou meer ruimte moeten gemaakt worden voor individuele therapie (naast groepstherapie). Beide benaderingen dienen wetenschappelijk vergeleken te worden wat betreft hun effectiviteit.
5. Er zijn ook geen wetenschappelijke gegevens over de effectiviteit van de combinatie van CGT en GET (ten opzichte van de geïnduceerde meerkost). Er zou een kosteneffectiviteitsstudie opgezet moeten worden, waarin een " monotherapeutische" aanpak vergeleken wordt met een gecombineerde aanpak. Buiten deze studie, en in afwachting van de resultaten van de analyse, dient voor één van beide therapieën gekozen te worden (naargelang de competentie van de het behandelende team en de voorkeur van de patiënt).
6. Het is aan te bevelen om systematisch gegevens over de ernstgraad van CVS te verzamelen, vb. op basis van de NICE-ernstcriteria of de criteria gesuggereerd door Reeves et al. (2006) zoals beschreven in het KCE-rapport. Echter, deze criteria zijn nog niet gevalideerd wat inhoudt dat een over- of onderschatting van de doelpopulatie mogelijk is. Het gebruik van deze criteria dient dus te gebeuren in de contekst van wetenschappelijk onderzoek, vooraleer ze definitief ingevoerd worden.

Het is ook wenselijk dat gegevens over comorbiditeit (vb. somatiform of anxio-depressief) geregistreerd worden, zodat op termijn het zorgmodel voor ernstig aangetaste patiënten kan geoptimaliseerd worden.

7. De therapeutische handleidingen gebruikt binnen de zorgnetwerken, dienen gebaseerd te zijn op handleidingen die in klinische studies hun effectiviteit bewezen hebben.
8. Om rationeel gebruik van de financiële middelen te verzekeren, wordt gesuggereerd om het medisch korps te informeren over de wel en niet uit te voeren diagnostische onderzoeken bij een vermoeden van CVS. De wijze waarop deze informatie verspreid dient te worden, dient overlegd te worden met de Federale Overheidsdienst Volksgezondheid. Er zou hiervoor eventueel een specifieke werkgroep opgericht kunnen worden binnen de Hoge Gezondheidsraad.
9. De literatuurreview van het KCE werd gelimiteerd tot CVS, en bevatte niet de vaak geassocieerde (co-)morbiditeiten zoals fibromyalgie, irritabel colon, anxio-depressieve syndromen etc. Het is de vraag of op termijn voor al deze aandoeningen afzonderlijke zorgnetwerken dienen ontwikkeld te worden, dan wel of gemeenschappelijke netwerken voor enkele van deze aandoeningen samen kunnen opgezet worden. In ieder geval dient vooraf onder Belgische experten een consensus gevormd te worden over de diagnostische criteria voor deze aandoeningen, gebaseerd op de wetenschappelijke literatuur. Nadien kan men evalueren hoe deze patiënten best gediagnosticeerd en behandeld worden, en dit kan met de betrokken partijen besproken worden.
10. Er is een nood om kinesitherapeuten en psychotherapeuten (privé of in een centrum voor Geestelijke Gezondheidszorg) op te leiden voor behandeling van CVS. De organisatie van deze vorming behoort niet tot de competentie van de Werkgroep CVS van de Hoge Gezondheidsraad. Wel dient opgemerkt te worden dat de referentiecentra, die immers beschikken over kennis en expertise ivm. CVS , een belangrijke rol zouden kunnen spelen in deze vorming.

Scientific summary

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GLOSSARY

AIDS	Acquired Immune Deficiency Syndrome
APT	Adaptative pacing therapy
CBT	Cognitive behavioural therapy
CCM	Chronic Care Model
CCT	Controlled clinical trial
CDC	Centers for Disease Control and Prevention
CFS	Chronic Fatigue Syndrome
CI	Confidence Intervals
CNCC	Clinical Network Co-ordinating Centre
CRD	Centre for Reviews and Dissemination
DMP	Disease Management Program
DN	Do nothing
DTH	Delayed-type hypersensitivity
EAS	Education and support
FTE	Full-time equivalent
GET	Graded exercise therapy
GP	General practitioner
GPwSI	GP with Special Interest
ICCC	Innovative Care for Chronic Conditions
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
INAMI/RIZIV	Institut National d'Assurance Maladie-Invalidité/Rijksinstituut voor Ziekte-en Invaliditeitsverzekering (The National Institute for Health and Disability Insurance or NIHDI)
LMDT	Local Multidisciplinary Team
MAOI	Monoamine oxidase inhibitor
MRI	Magnetic resonance imaging
NADH	Nicotinamide adenine dinucleotide
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NKCV	Nijmeegs Kenniscentrum Chronische Vermoeidheid
NNT	Number needed-to-treat
PCT	Primary Care Trust
PIFS	Post-infectious fatigue syndrome
PVFS	Postviral fatigue syndrome
QALY	Quality-adjusted life year
QoL	Quality of life
RCGP	Royal College of General Practitioners
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised controlled trial
RPE	Rating Perceived Exertion
RR	Relative risk
SD	Standard deviation
SG	Support group
SMC	Standard medical care

1 INTRODUCTION

1.1 DEFINITION

The Chronic fatigue syndrome (CFS) is a clinically defined condition characterised by severe, disabling fatigue in the absence of exertion. The fatigue is not improved by rest, may be worsened by physical or mental activities and is accompanied by a range of other symptoms such as headaches, sleep disturbance, cognitive difficulties and muscle pain.[1] The illness is marked by a dramatic decline in activity level leading CFS patients to perform at a significantly lower level of activity than they were able before the onset of the condition.

Currently, the aetiology of CFS remains unknown, although several factors have been suggested, including immunological, genetic, viral, neuroendocrine and psychological factors. However, it is actually unclear if they are initiating or predisposing factors or if they contribute to maintenance of a chronic illness. There is growing evidence that the condition is heterogeneous, and may not have a single or simple aetiology. Some regard it as a spectrum of symptoms that is triggered by a variety of factors in people who have an underlying predisposition.[2] While symptom severity varies among patients, Centers for Disease Control studies show that CFS can be as disabling as multiple sclerosis, lupus, rheumatoid arthritis, heart disease, end-stage renal disease or similar chronic conditions.[2]

The range of labels for CFS reflects the controversies about aetiology. Names have included post-viral syndrome,[3] myalgic encephalomyelitis[4] or epidemic neuromyasthenia.[5] Whether these different labels represent separate conditions or the same disorder is actually hotly debated.[6] Each label is unsatisfactory in some way: for example, fatigue is not the only component of CFS, making this label unattractive to some. Equally, myalgic encephalomyelitis implies a pathological abnormality that has not been demonstrated, and post-viral fatigue gives emphasis to what may have been only a triggering event.[6]

Chronic fatigue syndrome, as other unexplained syndromes (including fibromyalgia, Gulf War Syndrome, irritable bowel syndrome) is difficult to manage in practice. The classical approach to these controversial syndromes has centred on a model creating two camps–organic versus non-organic. Unfortunately, this model failed in achieving the desired understanding of these syndromes, most particularly in offering the therapist a practical and coherent approach to effective treatment.[7] Health psychology is asserting that the psychosocial experience of chronic illness is equally as important as its aetiology. So, modern health psychology employs a holistic approach (the notion that the mind and body are integrated) and as such, focuses on the integrated self as opposed to the divided self.[8] The *biopsychosocial* model suggests that once an illness has started its expression is affected by beliefs, coping styles, and behaviours, while consequential physiological and psychological effects act in some ways to maintain and/or modify the disease process. Environmental exposures and psychosocial modifiers affect the clinical expression of the condition, and ultimately, the outcome. This model accepts the reciprocal influences of disease and illness, and the clinical variability among individuals for a given medical condition.[9] This model opens avenues for research and treatment, from the somatic as well as the psychosocial point of view.

Spontaneous recovery is possible, for a part of affected people. Children with CFS have better outcomes than adults: the majority recover after a few months or a few years[10] whereas 20-50% of adults show improvement in the medium term and less than 10% return to pre-morbid levels of functioning.[11] There is some evidence to indicate that the sooner a patient is treated, the better chance of improvement.[11]

1.2 MANAGEMENT OF CFS IN BELGIUM AND CONTEXT OF THE CURRENT STUDY

In 1994, the Centers for Disease Control and Prevention (CDC, USA) published widely accepted criteria for a syndrome called 'chronic fatigue syndrome', which requires a minimal symptomatic period of 6 months, the exclusion of any underlying organic or psychiatric disorder which can cause chronic fatigue and four or more of the following

symptoms: unrefreshing sleep, lengthy malaise after exertion, impairment of concentration or short-term memory, sore throat, tender lymph nodes, multijoint pain, and headaches.[12]

CFS is identified by symptoms and disability and by excluding diseases that could explain these symptoms. There are no confirmatory physical signs or characteristic laboratory abnormalities.[13]

Nevertheless, a high diversity of diagnostic methods is used, some of them being considered as recommended (detailed patient history, physical examination, mental status screening and targeted laboratory screening tests) whereas only limited evidence is available for many other used diagnostic methods.[2] Many interventions have been used for the treatment, management and rehabilitation of patients with CFS from prolonged rests, to drug therapies and dietary supplements.

In Belgium, guidelines were proposed by the Conseil Supérieur de la Santé / Hoge Gezondheidsraad in 2000 (Appendix 1). The Belgian guidelines were based on consensus between the Belgian experts and were not subsequently validated. These guidelines encompass diagnostic and therapeutic strategies and precise a grading patients' management from general practitioners to referral centres offering a multidisciplinary approach. Five referral centres were created and financed to take CFS patients in charge (four centres dedicated to adults and one to children). Agreements between INAMI/RIZIV and these 5 centres were signed between April and October 2002 allocating an annual global budget of €1.6 millions for all centres. In 2006, a descriptive report gave an evaluation of these centres functioning.[14]

The agreements expire on September 30th 2008. INAMI/RIZIV has to decide on future financing rules for CFS patients care. To support its decision, INAMI/RIZIV asks for an updated evidence based knowledge related for diagnosis, therapy and alternatives in organisational modalities for CFS patients care. A cost analysis of recommendations is also required. Some specific questions can possibly be treated while performing the more general evaluation: the comparison of individual versus group therapy, the place of family doctors and medical specialists in the diagnosis and treatment trajectory, and how to guide efficiently the transfer from the rehabilitation stage to the chronic stage. This part of work was devoted to KCE in collaboration with the Conseil Supérieur de la Santé / Hoge Gezondheidsraad.

1.3 RESEARCH

The main objective of our study is to update the evidence based knowledge on diagnosis and treatment of CFS as well as the organisational alternatives to take CFS patients in charge. A following objective is to propose clinical guidelines to effectively diagnose and treat patients affected by CFS and to evaluate cost-effectiveness of various options for CFS management. The implementation of the final recommendations in Belgium should also be considered.

1.3.1 Research questions

In order to inform the INAMI/RIZIV adequately, the following research questions were formulated:

1. What are the existing definitions for CFS in adults and children?
2. What are the updated epidemiological data about CFS?
3. Does the evidence show that any particular diagnostic method or combination of diagnostic methods is effective in confirming CFS?
4. Does the evidence show that any particular intervention or combination of interventions is effective in treatment, management or rehabilitation of adults and children with a diagnosis of CFS?
5. Does the evidence show that any organisational alternatives are effective to take CFS patients in charge, including return to work /school?
    - What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work?
    - What patient characteristics best define improvement in functioning or positive outcomes in the CFS population? Where it occurs, how is

improvement in functioning related to the ability to engage in work activity?

6. What are the costs and possibly the cost-effectiveness of various options for CFS management?

1.3.2 Patient issues

Researchers also conducted a literature review about patient issues in order to identify and describe available information about patients' experiences with the illness, the relationships with others, the healthcare system or the administration as well as their expectations and/or complaints.

1.3.3 International comparison and Belgian data

The experience of other countries in management of CFS patients can be very interesting for Belgium. Comparing similarities and challenges and contrasting organizational, administrative and financing policies implemented might deepen our understanding and be very helpful.

Following questions will be addressed in relevant countries:

- How are CFS patients taken care of in other countries? Are there any specific structures or services available for these patients?
- Who is paying for these structures/services? What is the role of public funding? Private funding? Patient out-of-pocket?
- What are outcomes and advantages/disadvantages of these structures/services? What can Belgium learn from it?

In order to facilitate the comparison between the selected countries and Belgium, a brief overview of existing Belgian data will be given as well.

2 DEFINITION, DIAGNOSIS AND TREATMENT: A LITERATURE REVIEW

2.1 LITERATURE REVIEW: METHODOLOGY

2.1.1 Search methodology

Between October and November 2007, we have undertaken a literature review to identify relevant and published evidence to answer the key clinical questions. The review was broad and not restricted by intervention, diagnostic test or outcome, searching the following databases and websites:

- Cochrane Reviews database,
- Centre for Reviews and Dissemination (CRD) databases (University of York, UK) including DARE (Database of Abstracts of Reviews of Effects), NHS EED (NHS Economic Evaluation Database) and HTA (Health Technology Assessment) databases,
- Agency for Healthcare Research and Quality (AHRQ, USA), Australian National Health & Medical research Council Clinical Practice Guidelines, CDC (Centres for Disease Control, USA), CMA Infobase (Canada), Haute Autorité de Santé (HAS, France), Health Services /Technology Assessment Texts (HSTAT, USA), ICES (Institute for Clinical Evaluative Sciences, Canada), Institute for Clinical Evaluative Sciences, National Guideline Clearinghouse (USA), National Institute for Clinical Excellence (NICE, UK), New Zealand Guidelines Group, Royal College of Paediatrics and Child Health, Scottish Intercollegiate Guidelines Network (SIGN, UK),
- INAHTA (21/10/2007),
- Medline through Ovid (22/10/2007),
- Embase (23/10/2007).

The search strategy, developed by two researchers, is described in the appendix 2 (database, Mesh and/or "free terms"). Two reviewers independently assessed all titles and abstracts identified from the searches of electronic databases for potential relevance to the first five review questions. All papers that looked potentially relevant were retrieved in full as well as all papers for which titles and abstracts did not contain enough information to judge the relevance. All retrieved studies were then independently assessed by two reviewers for possible inclusion, using the inclusion criteria listed for each question below. Discrepancies were resolved by discussion.

We used the following criteria

- Selection criteria based on title and abstract (Level I screening):
  - Inclusion: systematic reviews and randomised controlled trials; patients fulfil criteria for CFS; adults, adolescents or children; any diagnostic method and/or therapy; any outcome (fatigue, anxiety, depression, return to work or school…).
  - Exclusion: duplicates; design (letter, comment, narrative review, case reports or editorials); mixed population (unable to separate CFS from other populations); pharmacokinetic and pharmacodynamic studies; studies focused on pathophysiology of CFS (lab findings/lab techniques); outcomes not extractable.
- Selection criteria based on full text (Level II screening):
  - Inclusion: systematic reviews (the most recent versions) and randomised clinical trials, studies with at least 30 patients, patients with CFS (subjects were adult, teenagers or children of all ages with a clinical diagnosis of Chronic Fatigue Syndrome according to Oxford criteria (Sharpe 1991), CDC (Fukuda 1994) or any other validated criteria, any diagnostic method and/or therapy, physical and psychological outcomes, return to school or to work.

- Exclusion: Other design (letter, comment, narrative review, case reports), other languages than English, Dutch, French or German, patients with other conditions.

In addition, the reference lists of the selected articles were searched for any missing relevant publications.

An additional search has been done for studies in progress on the site http://www.controlled-trials.com/mrct/search.html which includes a metaregister of controlled trials (including 13 databanks of trials in progress). The term "chronic fatigue syndrome" has been used.

2.1.2 Search results

2.1.2.1 Cochrane Systematic reviews

One Cochrane Systematic Review about effectiveness of exercise therapy and control treatments for CFS was published in 2004 and included in our review.

2.1.2.2 CRD databases

Relevant publications were searched in the CRD database (period 1996 - November 2007) with the term "chronic fatigue syndrome".

We found 23 references focused on chronic fatigue syndrome. They include 9 systematic reviews, 1 randomized control trial, 2 reports, 4 reviews, 1 cost-utility analysis, 1 cost-effectiveness analysis, 1 cost-study, 1 critically appraised topic and 3 study protocols. Among the 9 systematic reviews, only 5 fitted with selection criteria; of these, one systematic review covering all available diagnostic methods and interventions was performed by the Centre for Reviews and Dissemination (CRD Report 35)[1] published in February 2007 and its data collection stopped at May 2005. The evidence review was commissioned from the Centre for Reviews and Dissemination at the University of York, and was an update review based on a previous systematic review on the diagnosis, treatment and management of CFS in adults and children (CRD Report 22).[15] Much of the existing evidence being of poor quality, the review was restricted to RCTs and controlled trials.

2.1.2.3 Guidelines

Three guidelines were retrieved:

1. NICE Clinical Guideline 53 Chronic fatigue syndrome / myalgic encephalomyelitis (or encephalopathy), August 2007.[2]
2. NHS Plus Evidence based guideline project. Occupational aspects of the management of CFS: a national guideline, October 2006. [16]
3. Royal College of Paediatrics and Child Health. Evidence based guideline for the management of CFS in children and young people, December 2004.[17]

It is noteworthy that a NICE Clinical Guideline was developed by the National Collaborating Centre for primary Care (NCC-PC) and supported by the evidence review carried out by the University of York (CRD Report 35).[1] Searches were conducted in May/June 2005 with update searches being carried out in August 2006.

For children, an evidence based guideline for the management of CFS in children and young people was published in 2004 by the Royal College of Paediatrics and Child Health. The guideline primarily addressed paediatricians managing children and young people with symptoms consistent with a diagnosis of CFS. The patient population for the guideline is any child/young person up to the age of 18 referred to a paediatrician for assessment with debilitating fatigue.

Authors underline that the guideline does not cover the following clinical circumstances, patient groups or subject areas:

- The management of children and young people in primary care before referral to a paediatrician
- The long term inpatient management of patients (although the indications for inpatient admission are covered)

- The management of children and young people who may be chronically tired but who have a diagnosis of another medical or psychiatric illness which is causing the fatigue
- The management of co-morbid disorders
- Appraisal of the evidence underpinning theories of aetiology and biological/immunological markers of CFS or health economics of the condition.

The search strategy used for the guideline was based on that developed in the most recent evidence review undertaken by the Centre for Reviews and Dissemination[15] although the search was updated (until February 2004) and restricted to papers on children and young people.

Both CRD Report 35, NICE Clinical Guideline 53 for adults and RCPCH guideline for children and young people were considered as the base for our literature review, as well as the Cochrane Systematic Review about the effectiveness of exercise therapy. Additional studies published after the search strategy used in these publications were specifically searched in our own literature search strategy. However, we have searched the literature for material published from 2004 onwards, to avoid any missing in relevant publications.

2.1.2.4 HTA reports

No additional report was found.

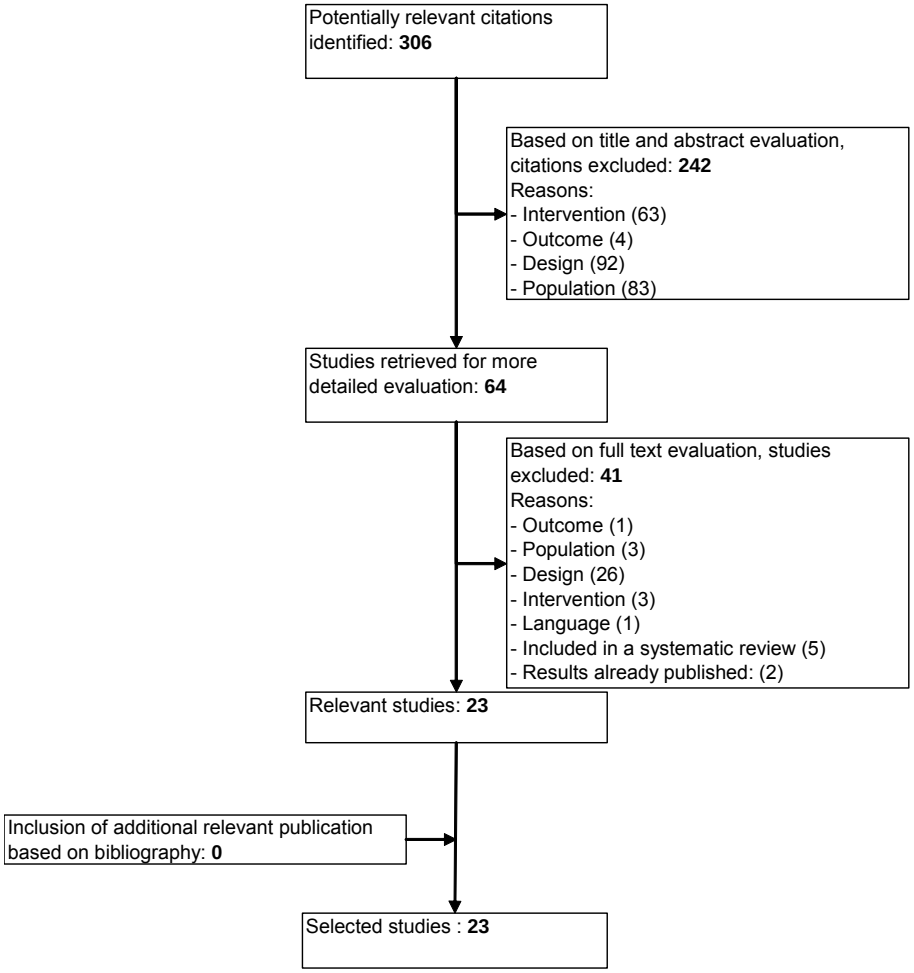
2.1.2.5 Studies in progress

Our search found 10 controlled trials completed or in progress (but not yet published) with chronic fatigue syndrome. The list of these trials can be found in appendix 2.

2.1.2.6 Literature review (period 2004-2007)

The primary search in Medline (search window: 2004 - Nov 2007) yielded 210 citations and the primary search in Embase (search window: 2004 - Nov 2007) yielded 96 additional citations (excluding duplicates). A total of 306 abstracts identified from electronic searches were screened against protocol-defined exclusion criteria. After screening of abstracts for exclusion criteria (Level I screening), 64 were accepted and these full-text papers were retrieved for more in-depth screening (Level II). During Level II screening of full-text papers, 41 were rejected, resulting in a total of 23 accepted studies (Figure 1). The most common reason for rejection was inappropriate design.

Figure 1. Literature search results flow chart



2.1.2.7 CDC website

The Centres for Disease Control (USA) have created a website devoted to Chronic fatigue syndrome (http://www.cdc.gov/cfs/). This website proposes a compilation of publications by the CDC 'CFS Public Health Research Program' from 1993 to present as well as a link to the PubMed database that includes peer reviewed articles on CFS. One meta-analyse about Cognitive Behavioural Treatment was available online 1 November 2007 (corrected proof) and retrieved.[18]

2.1.3 Critical appraisal: methodology

Relevant papers were reviewed to identify the best evidence to answer the key clinical questions. This process involved selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence.

The critical appraisal was done for systematic reviews and additional studies. Cochrane systematic reviews were not appraised according to their high quality of evidence.

2.1.3.1 Critical appraisal of systematic reviews concerning treatment

The following reviews have been considered for critical appraisal: Bagnall et al. (2007)[1], Reid et al. (2007)[11], Cho et al. (2005)[19], Ganz et al. (2002)[20]. The quality of systematic reviews was evaluated using the appropriate form of the Dutch Cochrane Collaboration (Form Vc)[a]. More details on the critical appraisal of the systematic reviews are given in Appendix 3.

[a] http://portal.iscientia.net/public/cebamfr/EBM/Pages/Downloads.aspx

2.1.3.2 Critical appraisal of (randomized) controlled trials concerning treatments

The quality of (randomized) controlled trials was evaluated using the appropriate form of the Dutch Cochrane Collaboration (Form II)[a] (see Appendix 4). Based on this appraisal, a level of evidence (good, moderate or weak) was assigned to each of the included studies according to Guyatt' recommendations.[21] More details are given in Appendix 5.

2.2 DEFINITIONS OF CHRONIC FATIGUE SYNDROME

Evidence for the Question 1: What are the existing definitions for CFS in adults and children?

Chronic fatigue syndrome is a complex illness defined by self-reported unexplained disabling fatigue and a combination of non-specific accompanying symptoms. Similar disorders have been described for at least two centuries and have been variously named neurasthenia, myalgic encephalomyelitis, Akureyri disease, post-viral fatigue, royal free disease, chronic Epstein-Barr, yuppie flu, yuppy flu and chronic mononucleosis. The first formal case definition, published in the United States in 1988[22], suggested the name "chronic fatigue syndrome" or CFS, which was retained in subsequent Australian[23] and British[24] case definitions.

2.2.1 Main definitions of chronic fatigue syndrome[b]

An internationally accepted CFS definition was published in 1994 and provides the current standard for diagnosis CFS.[12] Although, the 1994 case definition comprises the current international standard for classification of research subjects as CFS, there are substantial differences between all the definitions and it is important to compare them in order to better understand results of research studies.

2.2.1.1 Chronic fatigue syndrome-the CDC definition (1988)[22]

For diagnosis, both major criteria must be present, plus the following minor criteria: (1) at least 6 of 11 symptoms and at least 2 of 3 physical signs or (2) at least 8 of 11 symptoms.

MAJOR CRITERIA

1. New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that does not resolve with bed rest, and that is severe enough to reduce or impair average daily activity below 50 percent of the patient's premorbid activity level for a period of at least 6 months
2. Exclusion of other clinical conditions that may produce similar symptoms (e.g., malignancy, autoimmune disease, chronic psychiatric disease, and chronic inflammatory disease, among others)

MINOR CRITERIA

Symptom criteria

1. Low-grade fever (i.e. 37.5°C to 38.6°C)
2. Sore throat
3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution
4. Unexplained generalized muscle weakness
5. Muscle discomfort or myalgia
6. Prolonged (≥ 24 hours) generalized fatigue after exercise
7. Generalized headaches
8. Migratory arthralgia without joint swelling or redness

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[b] These definitions are on CDC Website : http://orwh.od.nih.gov/cfs/aboutDiagnosis.html

9. Neuropsychologic complaints (one or more of the following: photophobia, visual scotomas, forgetfulness, irritability, confusion, difficulty concentrating, depression)
10. Sleep disturbance
11. Acute onset (over a few hours to a few days).

Physical criteria (documented by a medical practitioner twice at least 1 month apart)

1. Low-grade fever
2. Nonexudative pharyngitis
3. Cervical or axillary lymphadenopathy
4. The 1988 chronic fatigue syndrome (CFS) working case definition did not effectively distinguish CFS from other types of unexplained fatigue. For this reason, it was decided during a 1993 meeting of CFS investigators to develop a logical revision of that definition which will be presented in the section 2.2.1.4.

2.2.1.2 CFS-the Australian definition (1990)[23]

The Australian criteria consisted of the following symptoms:

1. Chronic persisting or relapsing fatigue of a generalized nature, exacerbated by minor exercise, causing significant disruption of usual daily activities, and present for more than 6 months
2. Neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks which were easily accomplished before the onset of the syndrome; new onset of short term memory impairment
3. No alternative diagnosis reached by history, physical examination, or investigations over a 6-month period

2.2.1.3 CFS-the British definition (1991)[24]

The "Oxford criteria", developed in 1991 by a panel of clinicians and scientists, defined two broad syndromes: chronic fatigue syndrome and post-infectious fatigue syndrome (PIFS). CFS was defined by the following characteristics:

1. Fatigue is the principal symptom.
2. It is a syndrome of definite onset that is not lifelong.
3. Fatigue is severe, disabling, and affects physical and mental functioning.
4. Fatigue has been present for a minimum of 6 months, during which it was present for more than 50 percent of the time.
5. Other symptoms may be present, particularly myalgia, mood, and sleep disturbance.
6. Exclusion criteria included patients with established medical conditions known to produce chronic fatigue and those with certain psychiatric disorders (substance abuse, eating disorders, organic brain disease).

PIFS was considered a subtype of CFS that either follows an infection or is associated with a current infection. PIFS fulfils all the criteria for CFS as well as the following:

1. Definite evidence of infection at onset or presentation
2. Present for a minimum of 6 months after onset of infection
3. Infection corroborated by laboratory evidence

2.2.1.4 CFS-the international definition (1994) [12]

The revision of the 1988 CDC case definition was obtained through a consensus viewpoint from many of the leading CFS researchers and clinicians (an international collaborative group that included authors of the previous case definitions) including input from patient group representatives.

This revised definition remains currently the accepted research definition, also known as the Fukuda definition, and was based on the presence of the following:

1. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities
2. The concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue:
    - Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities
    - Tender cervical or axillary lymph nodes
    - Sore throat
    - Muscle pain
    - Multijoint pain without joint swelling or redness
    - Headaches of a new type, pattern, or severity
    - Unrefreshing sleep
    - Postexertional malaise lasting more than 24 hours

In the revised definition, chronic fatigue syndrome is treated as a subset of chronic fatigue, a broader category defined as unexplained fatigue of greater than or equal to six month's duration. Chronic fatigue in turn, is treated as a subset of prolonged fatigue, which is defined as fatigue lasting one or more months. The expectation is that scientists will devise epidemiologic studies of populations with prolonged fatigue and chronic fatigue, and search within those populations for illness patterns consistent with CFS.

The 1994 CDC criteria were recently reviewed with the aim of improving case ascertainment for research. The exclusion criteria were clarified and the use of specific instruments for the assessment of symptoms was recommended.[13] The International Chronic Fatigue Syndrome Study Group elaborated the following exclusionary criteria:

- Permanent medical exclusions:

a. Organ failure (e.g., emphysema, cirrhosis, cardiac failure, chronic renal failure)
b. Chronic infections (e.g., AIDS, hepatitis B or C)
c. Rheumatic and chronic inflammatory diseases (e.g., systemic lupus erythematosis, Sjorgren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis)
d. Major neurologic diseases (e.g., multiple sclerosis, neuromuscular diseases, epilepsy or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurologic deficits)
e. Diseases requiring systemic treatment (e.g., organ or bone marrow transplantation; systemic chemotherapy; radiation of brain, thorax, abdomen, or pelvis)
f. Major endocrine diseases (e.g., hypopituitarism, adrenal insufficiency)
g. Primary sleep disorders (e.g., sleep apnea, narcolepsy)

- Temporary medical exclusions:

Conditions discovered at onset or initial evaluation (e.g., effects of medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, active infection)

a. Conditions that resolved (e.g., pregnancy until 3 months post-partum, breastfeeding, major surgery until 6 months post-operation, minor surgery until 3 months post-operation, major infections such as sepsis or pneumonia until 3 months post-resolution)
b. Major conditions whose resolution may be unclear for at least 5 years (e.g., myocardial infarction, heart failure)

c. Morbid obesity (body mass index > 40)

- Permanent psychiatric exclusions:

Lifetime diagnoses of bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementias of any subtype, organic brain disorders, and alcohol or substance abuse within 2 years before onset of the fatiguing illness.

2.2.1.5 *Myalgic encephalomyelitis/CFS—the Canadian definition (2003)* [25]

The 2003 Canadian definition is more stringent and was developed by an international clinical CFS team. This definition encompasses:

1. Fatigue: Significant degree of new-onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.
2. Post-exertional malaise and/or fatigue: Loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional fatigue, malaise and/or pain, and a tendency for other symptoms to worsen. A pathologically slow recovery period (more than 24 hours).
3. Sleep dysfunction: Unrefreshing sleep or poor sleep quality; rhythm disturbance such as reversed or chaotic diurnal sleep rhythms.
4. Pain: Significant degree of myalgia experienced in muscles and/or joints; often widespread and migratory in nature. Often, significant headaches of new type, pattern, or severity.
5. Neurological/cognitive manifestations: Two or more of the following: confusion; impairment of concentration and short-term memory consolidation; disorientation; difficulty with information processing, categorizing, and word retrieval; and perceptual/sensory disturbances. Possible cognitive or sensory overload (e.g., photophobia, hypersensitivity to noise) and/or emotional overload leading to relapses.
6. At least one symptom from two of the following categories:
   a. Autonomic manifestations: Orthostatic intolerance, light-headedness, extreme pallor, nausea and irritable bowel syndrome, urinary frequency and bladder dysfunction, palpitations with or without cardiac arrhythmia, exertional dyspnea.
   b. Neuroendocrine manifestations: Loss of thermostatic stability, heat/cold intolerance, marked weight change, loss of adaptability and worsening of symptoms with stress.
   c. Immune manifestations: Tender lymph nodes; recurrent sore throat; flu-like symptoms; general malaise; new sensitivities to food, medications, and/or chemicals.
7. Illness persisting for at least 6 months. Usually acute onset, but may be gradual.

2.2.1.6 *Update of the literature review about definition*

The updating of literature review (2004-2007) did not add new papers about validated CFS definitions.

However, it is important to underline that an *International CFS Study Group* had identified ambiguities in the CDC-1994 definition that contribute to inconsistent case identification.[13] Consequently, members of this group recommended revisions for improving the precision of case ascertainment for research studies. While intended to apply primarily to the research setting, their recommendations would also be useful for health care providers because they suggest standardized instruments to record and to measure the key symptom domains and the disability associated with CFS.[13]

In a large population-based case control study (Wichita, USA), Reeves et al. (2005) have implemented these recommendations and defined CFS on the basis of scores from standardized and validated instruments that assess the major dimensions of the illness as specified by the 1994 CFS case definition.[26]

Validated instruments that were used were:[26]

- the Multidimensional Fatigue Inventory (MFI) to evaluate fatigue status; [27]
- the Medical Outcomes Survey short form-36 (SF-36) to measure functional impairment]; [28]
- the CDC Symptom Inventory to assess frequency and severity of the 8 CFS defining symptoms. [29]

Functional impairment was defined as scores ≤ 70 on the physical function **or** ≤ 50 on the role physical **or** ≤ 75 on the social function **or** ≤ 66 on the role emotional subscales of the SF-36.

Severe fatigue was defined as scores ≥ 13 on the general fatigue **or** ≥ 10 on the reduced activity subscales of the MFI.

Finally, the accompanying symptom complex was defined as reporting the occurrence of ≥ 4 of 8 symptoms **and** scoring ≥ 25 on the Symptom Inventory Case Definition subscale.

However, by applying these three questionnaire cut-off scores, a larger group of functional impaired persons was defined as compared to the 1994 CFS case definition. More research is necessary on the use of validated instruments to define CFS.

Key points

- **The internationally accepted CFS definition was proposed by Fukuda (CDC) in 1994 and provides the current standard for diagnosis CFS:**
- **Clinically evaluated, medically unexplained fatigue of at least 6 months' duration that is of new onset; not a result of ongoing exertion; not substantially alleviated by rest; results in substantial reduction in previous levels of activity.**
- **The occurrence of four or more of the following symptoms: subjective memory impairment, tender lymph nodes, sore throat, muscle pain, joint pain, headache, unrefreshing sleep, postexertional malaise (> 24 hours).**
- **Exclusion criteria: active, unresolved, or suspected disease likely to cause fatigue (organ failure, chronic infections, rheumatic and chronic inflammatory diseases, major neurologic diseases, diseases requiring systemic treatment, major endocrine diseases); primary sleep disorders; psychotic, melancholic, or bipolar depression (but not uncomplicated major depression); anorexia or bulimia nervosa; alcohol or other substance misuse; and severe obesity.**
- **Using strict definition for CFS based on Fukuda criteria is advocated.**

2.2.2 Validation of the existing case definitions for CFS

Seventy-four studies were reviewed and summarized in the NICE report for validation of case definitions.

The CDC 1994 case definition was most often investigated (41 studies), followed by CDC 1988 (16 studies), Oxford (6 studies), Australian (3 studies) and the Dowsett and Canadian criteria (1 study each).

The evidence to substantiate the existing case definitions of CFS was severely limited: studies that compared findings in patients with CFS with findings in healthy individuals or patients with other conditions do not provide an adequate basis for validation of any particular case definition. The reason for this is that most have selected patients based on the case definition that often includes symptoms or findings that are then compared. This would make most studies level 2B or lower. Few studies involved large unselected populations or used comprehensive assessment methods to evaluate whether a distinct group of findings characterised and differentiated CFS from other conditions. No studies were able to establish the superiority of one existing case definition over another.

Studies conducted before 2001 that compared findings in patients with CFS with findings in healthy individuals or patients with other conditions did not provide an adequate basis for validation of any particular case definitions. Studies published later came to the following conclusions:

Adults

- Evidence to substantiate existing case definitions of CFS is limited. No studies have established the superiority of one case definition on another (Evidence quality 2B).
- Community-based studies have indicated that patients meeting CDC 1994 criteria form a more heterogeneous group than patients meeting CDC 1988 criteria (Evidence quality 2B).
- There is currently limited evidence that patients meeting Dowsett ME or the Canadian criteria are more likely to have more symptoms than those meeting CDC 1994 criteria (Evidence quality 2B).

Children

- Evidence is very limited to substantiate existing case definitions (Evidence quality 2B).
- One study has shown that adolescents who meet CDC 1994 criteria for CFS had higher anxiety, depression, somatisation, school absence and illness attribution scores than those suffering with migraine or healthy controls (Evidence quality 2B).

2.2.3 Duration of symptoms to diagnose CFS

CFS is defined as persistent or relapsing fatigue of at least **6-months'** duration, that is not alleviated by rest, and that causes substantial reduction in activities. This fatigue must be accompanied by at least 4 of 8 case defining symptoms (CDC-1994 criteria).

Besides this international definition, the Guidelines Development Group of NICE has proposed a different threshold of symptoms' duration: "after ruling out other possible likely causes of the symptoms, a diagnosis of CFS should be made in an adult after 4 months **or** after 6 months".[2] The two propositions were accepted by consensus between experts. However, NICE finally recommended making diagnosis of CFS when symptoms have persisted for 4 months.[2] As no corroborating evidence is endorsing this criterion, this will not be recommended in Belgium. This may lead to over diagnosis, not awaiting spontaneous natural regression (e.g. post-viral asthenia).

In the same way, NICE recommended a shorter duration of symptoms (3 months) to diagnose CFS in children and adolescents, arguing that 6 months of symptoms is too long for young persons.[2] This argument has never been tested and seems to be particularly troublesome since the syndrome in adolescents often resolves spontaneously and a premature diagnosis can lead to a "learned illness" state.

2.2.4 Commonly observed symptoms in CFS and similarities to other disorders

2.2.4.1 Other commonly observed symptoms in CFS

In addition to the eight CFS-defining symptoms,[12] some people with CFS may experience other symptoms. The frequency of occurrence of these symptoms varies among patients. These symptoms include:[30]

- irritable bowel, abdominal pain, nausea, diarrhea or bloating
- chills and night sweats
- brain fog
- chest pain
- shortness of breath
- chronic cough
- visual disturbances (blurring, sensitivity to light, eye pain or dry eyes)

- allergies or sensitivities to foods, alcohol, odors, chemicals, medications or noise
- difficulty maintaining upright position (orthostatic instability, irregular heartbeat, dizziness, balance problems or fainting)
- psychological problems (depression, irritability, mood swings, anxiety, panic attacks)
- jaw pain
- weight loss or gain

According to CDC,[30] clinicians will need to consider whether such symptoms relate to a comorbid or an exclusionary condition; they should not be considered as part of CFS other than they can contribute to impaired functioning.

2.2.4.2 Similar syndromic illnesses

A number of syndromic illnesses have several clinical features that overlap of those of CFS. These include fibromyalgia syndrome, neurasthenia, multiple chemical sensitivity, and post-infectious fatigue (e.g., chronically fatiguing illness following infectious mononucleosis). Although these illnesses may present with a primary symptom other than fatigue, chronic fatigue is commonly associated with all of them.[30] Whereas scientifics clearly distinguish fibromyalgia syndrome from chronic fatigue syndrome, these two syndromes are frequently considered as interchangeable by the public. Patients' associations offering general information about chronic syndromes represent together these two distinct disorders. Examples come from:

- Association belge du syndrome de fatigue chronique et de fibromyalgie (http://users.skynet.be/ab-cfs-fm/)
- Agence wallonne pour l'intégration des personnes handicapées (http://www.awiph.be:81/Record.htm?idlist=2&record=323412414169)
- L'Association Française du Syndrome de Fatigue Chronique et de Fibromyalgie (http://asso.nordnet.fr/cfs-spid/)

However, this report focuses specifically on chronic fatigue syndrome and excludes literature about fibromyalgia.

2.2.4.3 Similar medical and psychiatric disorders

A large number of clinically defined medical and psychiatric disorders (many of which can be treated and/or cured) cause fatiguing illness similar to CFS. The presence of any of these diseases precludes a diagnosis of CFS until the condition has been successfully treated and can no longer explain the fatigue and other symptoms. Examples of such diseases include endocrine (diabetes and hypothyroidism), neurologic (multiple sclerosis, stroke, sleep apnoea, and narcolepsy), rheumatic and chronic inflammatory (Sjögren's syndrome, rheumatoid arthritis, inflammatory bowel disease), infectious (hepatitis C, AIDS, mononucleosis), organ-specific (heart, emphysema, and hypertension), iatrogenic (reactions to prescribed medications) diseases as well as cancers. Examples of psychiatric disorders include bipolar disorders, psychoses, melancholic depression, eating disorders, and alcohol or substance abuse.[30]

2.2.5 Severity

A severity grading was proposed by the NICE Guideline Development Group distinguishing mild, moderate and severe CFS patients.

Mild CFS –Individuals are mobile, can care for themselves and can do light domestic tasks with difficulty. The majority will still be working. However, in order to remain in work they will probably have stopped all leisure and social pursuits, often taking days off. Most will use the weekend to cope with the rest of the week.

Moderate CFS –Individuals have reduced mobility and are restricted in all activities of daily living, often having peaks and troughs of ability, dependent on the degree of symptoms. They have usually stopped work and require rest periods, often sleeping in the afternoon for one or two hours. Sleep quality at night is generally poor and disturbed.

Severe / Very Severe CFS - Will be able to carry out minimal daily tasks only (e.g. face washing, cleaning teeth) or are unable to mobilise and do any of these for themselves. Have severe cognitive difficulties and be wheelchair dependent for mobility. These people are often unable to leave the house except on rare occasions with severe prolonged after-effect from effort. They may also be in bed for the majority of the time and are often unable to tolerate any noise, and are generally extremely sensitive to light.

This classification, based on a consensus between NICE experts, was not tested in empirical researches. It could be difficult to be operational, both for researchers and clinicians. Reeves et al. have defined CFS on the basis of scores from standardized and validated instruments (see 2.2.1.6.).[26] With these validated instruments, they also tried to differentiate CFS patients on a severity scale

So, they defined:

- severe fatigue as ≥ 13 of the MFI general fatigue or ≥ 10 reduced activity scales (median scores);
- substantial functional impairment as scores ≤ 70 on the physical function, or ≤ 50 on role physical, or ≤ 75 on social function, or ≤ 66.7 on role emotional subscales of the SF-36 (lower than the 25th percentile of published US population);
- subjects having substantial accompanying symptoms as reporting ≥ 4 symptoms and scoring ≥ 25 on the Symptom Inventory Case Definition Subscale.

However, by applying these criteria, a larger group of functional impaired persons was defined as compared to the 1994 CFS case definition. More research is necessary on the use of validated instruments to define CFS.

2.3 DIAGNOSIS OF CHRONIC FATIGUE SYNDROME

Evidence for the Question 3: Does the evidence show that any particular diagnostic method or combination of diagnostic methods is effective in confirming CFS?

There are currently neither physical signs nor diagnostic laboratory tests that identify CFS specifically. However, investigations have a particularly important role in ruling out the presence of alternative diseases.

Without clear recommendations about which tests to prescribe, the number and type of tests performed vary from physician to physician. But a number of diagnostic tests, some of which being offered commercially, have no demonstrated value for the diagnosis of CFS.[30] Consequently, it is really important to review the usual diagnostic tests in order to propose evidence based recommendations.

2.3.1 Literature review by NICE

In the literature review conducted by NICE, twenty-eight studies met inclusion criteria for diagnosis. All but six were of a low quality of evidence, being case-control studies or consensus guidelines (quality level 3 or 4).

Among the 6 studies having a higher quality level, 3 were graded as 'moderate quality' reported that the tests evaluated showed no difference between CFS patients and controls:

- a human T-cell leukaemia virus polymerase chain reaction analysis (HTLV PCR analysis);[31]
- a comparison between three retroviral laboratory tests: Polymerase Chain Assay (PCR) with PCR modified assay and culture for foamy cell cytopathic effect;[32]
- measure of natural killer cell activity in blood sample in lytic units (IU).[33]

The other three all reported that the tests were able to distinguish CFS patients from controls.[34,35,36] All three of these studies were about the head-up tilt test, and were published by the same group of authors. Three other studies graded as 'low quality of

evidence' published by the same authors also indicated that the head up tilt test was able to discriminate CFS patients from healthy controls.[37,38,39] However, NICE has not found any evaluations of the head up tilt test that did not find results in its favour, or any evaluations by other authors, which may suggest the possibility of publication bias.

Other diagnostic tests found to discriminate between CFS and non-CFS individuals but only with low quality of evidence:

- fibrinogen, prothrombin fragment 1+2, thrombin-anti-thrombin complexes, soluble fibrin monomer (SFM) and platelet activation (CD62P and ADP)
- auditory brainstem responses (ABR); stapedial contraction as measured by a prolonged decay test using impedance audiometry.

Diagnostic tests unable to discriminate between CFS and non-CFS patients but only with low quality of evidence:

- activation of the 2,5A synthetase/ribonuclease latent (RNase L) and RNA-regulated protein kinase (PKR) antiviral pathways.[40]
- the RNase L isoform ratio (37/83 kDa) in peripheral blood mononuclear cells: in the absence of acute infection or chronic inflammation, a high RNase L ratio could distinguish CFS patients from healthy volunteers;[41] however, this ratio has a high variability (while fatigue remained stable) and a poor reproducibility in patients with CFS.[42]

2.3.2 Incremental search about diagnostic tests

The update of NICE literature review led us to consider a more recent paper about the use of head-up tilt test, written by Jones et al. (2005)[43] and a comment published later by Rowe and Lucas (2007).[44]

Jones et al. (2005)[43] found that the stand-up test, frequently performed in clinical practice to screen for primary autonomic dysfunction in patients with fatiguing illnesses did not identify people with abnormal head-up tilt results. Authors conclude that an office stand-up tilt is not useful in the evaluation of orthostatic instability in CFS patients except as a screening tool for autonomic dysfunction in severely compromised individuals. However, according to Rowe (2007),[44] researchers had to exclude 86% of their original CFS population subjects with other medical conditions and subjects being treated with medications used to treat orthostatic intolerance. Consequently, the sample of CFS patients submitted to the test was entirely too small (10 CFS patients / 25 non-fatigued controls) to allow firm conclusions to be drawn about the prevalence of orthostatic intolerance overall in those with CFS, or about the relative prevalence of postural tachycardia or neurally mediated hypotension in this group.

In Belgium, guidelines proposed by the Conseil Supérieur de la Santé / Hoge Gezondheidsraad in 2000 (Appendix 1) encompass other diagnostic strategies such as imaging techniques (like MRI, PET-scan, or SPECT-scan) or polysomnographic assessment of sleep. According to these guidelines, imaging techniques should not be performed unless required for diagnosis of a suspected exclusionary condition (e.g., MRI to rule out suspected multiple sclerosis) or unless they are part of a scientific study. These expensive techniques do not confirm a diagnosis of CFS and should be avoided in routine practice. On the other hand, these Belgian guidelines propose to conduct assessment of sleep to exclude primary or chronic sleep disturbances, major depression, schizophrenia or other psychiatric conditions.

However, CRD Report 35 did not mention nor assess the effectiveness of this diagnostic procedure. Consequently, a literature review about sleep disturbances in CFS patients and the value of polysomnographic assessment of sleep as diagnosis test was conducted in May 2008 combining MESH terms as following: 'Polysomnography AND chronic fatigue syndrom' (Medline; access: OVID). From 28 articles retrieved, only 3 satisfied our inclusion criteria (see section 2.1.1.): Majer et al. (2007)[45], Neu et al. (2007)[46] and Reeves et al. (2006)[47].

In the studies of Majer et al.[45] and Neu et al.,[46] it is concluded that sleep efficiency did not differ significantly between CFS patients (in which primary sleep disorders had already been excluded) and controls (healthy volunteers) even if sleep quality perceptions were poorer rated in CFS group. The most striking finding of these studies is the *absence* of readily identifiable differences in objective, polysomnographically defined sleep parameters between subjects with CFS and non-fatigued controls. Similarly, there were no differences between persons with CFS and non-fatigued controls with respect to daytime multiple sleep latency tests. Consequently, there is no evidence that altered sleep architecture is a critical factor in CFS.

In the population-based study of Reeves et al.,[47] 18% of patients with possible CFS, sent to the sleep lab to exclude primary sleep disorders, had previously unrecognized clinically severe apnea or narcolepsy. However, in 7% of the healthy controls primary sleep disorders were also discovered; the difference was not significantly different. Since this study concerned only a small patient group (43 CFS patients and 43 healthy controls), the authors conclude that additional, sufficiently powered, studies with possible CFS cases identified from the population should be conducted.

In conclusion, while awaiting larger studies on this subject, it can be advised to conduct polysomnography in possible CFS patients in which anamnesis points to a considerable risk of severe apnea or other primary sleep disorders.

2.3.3 Recommendations for diagnosis

These recommendations are largely based on NICE report; moreover, they take into account results obtained from our own incremental search about specific diagnostic procedures.

CFS can be diagnosed in a primary care setting. The 1994 International Case Definition for CFS forms the basis of a reliable diagnostic algorithm for CFS, particularly in adults.

2.3.3.1 Symptoms that may indicate CFS

By definition, all people suffering from CFS experience severe, all-encompassing mental and physical fatigue that is not relieved by rest and that has lasted longer than six months. The fatigue is accompanied by characteristic symptoms. To be diagnosed with CFS, patients must experience significant reduction in their previous ability to perform one or more aspects of daily life (work, household, recreation or school).

Clinicians should consider a diagnosis of CFS if these two criteria are met: [2]

1. Unexplained, persistent fatigue that is not due to ongoing exertion, is not substantially relieved by rest, is of new onset (not lifelong) and results in a significant reduction in previous levels of activity.

2. Four or more of the following symptoms are present for six months or more:

- cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding, planning/organising thoughts and information processing
- postexertional malaise (extreme, prolonged exhaustion and exacerbation of symptoms following physical or mental exertion)
- unrefreshing sleep
- muscle pain
- multijoint pain without swelling or redness
- headaches of a new type or severity
- sore throat
- tender cervical or axillary lymph nodes

The symptoms of CFS fluctuate in severity and may change in nature over time.

Consider other diagnoses or co-morbidities before attributing clinical features to CFS

In particular, investigate these 'red flag' features:

- localising/focal neurological signs
- signs and symptoms of inflammatory arthritis or connective tissue disease
- signs and symptoms of cardiorespiratory disease
- significant weight loss
- sleep apnoea
- clinically significant lymphadenopathy.

The Royal College of Paediatrics and Child Health guideline stated that a young patient who is referred with debilitating fatigue for assessment should be given an initial opinion of 'generalised fatigue'. A child or young person who has symptoms suggestive of CFS should be referred to a paediatrician for assessment to exclude other diagnoses within 6 weeks of presentation.[17]

2.3.3.2 Diagnostic investigations

STANDARD TESTS TO PERFORM

The following tests constitute a typical standard battery to exclude other causes of fatiguing illness:[2]

- urine analysis for protein, blood and glucose
- full blood count and erythrocyte sedimentation rate or plasma viscosity
- serum urea, creatinine, electrolytes and calcium
- liver function
- thyroid function (TSH and free T4)
- C-reactive protein
- blood glucose, preferably fasting
- creatine kinase
- assessment of serum ferritin levels (children and young people only).

Use clinical judgement to decide on additional tests to exclude other diagnoses. For example, if a patient has low levels of serum albumin together with an above-normal result for the blood urea nitrogen test, kidney disease would be suspected. The physician may choose to repeat the relevant tests and possibly add new ones aimed specifically at diagnosing kidney disease. If autoimmune disease is suspected on the basis of initial testing and physical examination, the physician may request additional tests, such as for antinuclear antibodies.[30]

TESTS THAT SHOULD BE AVOIDED

As evidenced by literature review, **do not do**:[30,2]

- tests for serum ferritin in adults, unless other tests suggest iron deficiency
- tests for vitamin B_{12} deficiency or folate levels, unless a full blood count and mean cell volume show a macrocytosis
- tests for activation of 2,5A synthetase/ribonuclease latent (RNase L) and RNA-regulated protein kinase (PKR) antiviral pathways
- immunologic tests, including cell profiling tests such as measurements of natural killer cell (NK) number or function, cytokine tests (e.g., interleukin-1, interleukin-6, or interferon), or cell marker tests (e.g., CD25 or CD16)
- serological testing, unless there is an indicative history of an infection; if so, consider tests for:
  - chronic bacterial infections, such as borreliosis
  - chronic viral infections, such as HIV or hepatitis B or C

- acute viral infections, such as infectious mononucleosis (anti-Epstein Barr antibodies).

Before more research will be available to give evidence on their utility and their ability to discriminate CFS patients from controls, **do not do** the following tests routinely:

- the head-up tilt test
- auditory brainstem responses
- electrodermal conductivity
- polysomnographic assessment of sleep (awaiting confirmation of the recent data from Reeves et al. (2006)[47] in larger population studies), except if the anamnesis suggested a primary sleep disorder. In this latter case, a clinical assessment by a sleep physician is critical to decide on the usefulness of a polysomnography.

Reconsider the diagnosis if the person has none of the following symptoms:

- post-exertional fatigue or malaise
- cognitive difficulties
- sleep disturbance
- chronic pain.

Tests should not be repeated as is often the case in current practice due to e.g. medical shopping.

Key points

- **The diagnosis is a clinical one. No discriminating diagnostic tests are currently available, for adults or for children and young people;**
- **Before making the diagnosis, it is important to exclude alternative and common diagnoses, such as endocrine diseases or mood disorders;**
- **To exclude alternative diagnoses, a battery of tests is recommended (see Standard tests to perform) whereas a lot of diagnostic procedures should be avoided (see Tests that should be avoided) according to the absence of evidence about their ability to discriminate CFS patients from non-CFS patients;**
- **Using strict definition for CFS based on Fukuda criteria is advocated;**
- **NICE recommended making diagnosis of CFS when symptoms have persisted for 4 months. As no scientific evidence is endorsing this criterion, this recommendation should not be implemented in Belgium before a validation against current definitions;**
- **Tests should not be repeated as is often the case in current practice due to e.g. medical shopping;**
- **It can be recommended to refer children and young people to a paediatrician for assessment to exclude other diagnoses within 6 weeks of suggestive symptoms (RCPCH recommendations);**
- **A child who is referred with debilitating fatigue for assessment should be given an option of "generalised fatigue";**
- **Though it has been suggested to make the diagnosis in children as soon as after 3 months of debilitating fatigue, a better scientific underpinning of this criterion is absolutely recommended before adopting it in a new definition.**

2.4 EPIDEMIOLOGICAL DATA ABOUT CFS

Epidemiological studies and their findings are likely to differ according to the setting in which they were conducted, whether fatigue as a symptom, chronic fatigue or CFS was studied, the definition of CFS used and the rigorousness of the efforts made to rule out alternative medical explanations.[48] Comparisons between studies having studied prevalence of CFS are summarized in Table 1.

2.4.1 Prevalence of CFS in adults

2.4.1.1 Primary care studies

In the early 1990, many of the studies conducted among primary care attendees had small sample sizes and inappropriate sampling procedures.[48]

Among studies conducted in large samples, Wessely et al. examined the prevalence of CFS in primary care in England.[49] Their prospective study aimed to determine the prevalence of CFS in 1 199 primary care attendees with viral infection and 1 177 controls (non viral infectious). A follow-up rate of 84% was managed at 6 months. At 6 months, 9.9% of the infectious group and 11.7% of the control group reported chronic fatigue. However, CFS was less common, with point prevalence ranging from 0.1% (unmodified 1988 CDC criteria) to 0.7% (British definition criteria), when co-morbid psychiatric disorders were excluded.

Another study was conducted in America in a cohort of 1 000 patients in a primary care clinic in an urban, hospital-based general medicine practice.[50] The point prevalences of CFS were there 0.3% (95% confidence interval [CI], 0% to 0.6%), 0.4% (95% CI, 0% to 0.8%), and 1.0% (95% CI, 0.4% to 1.6%) using the 1988-CDC, British, and Australian case definitions, respectively. Authors conclude that while chronic, debilitating fatigue is common in medical outpatients, CFS is relatively uncommon and prevalence substantially depends on the case definition used.

2.4.1.2 Community-based studies

Before 1994, two peer-reviewed studies have made population-based estimates of the prevalence of chronic fatigue syndrome. The first study, which was conducted in Australia, relied on sollicitation of medical-practitioner referrals to identify persons with 1988-CDC criteria.[23] Using this definition, the researchers estimated the point prevalence as 37 cases per 100 000 population. The second study, conducted in the United States, was based on data from a nationwide population-based mental health survey of 13 000 persons[51] using Diagnostic Interview Schedule (DIS) to approximate the CFS case definition. Only one case of CFS was identified, for an estimated prevalence of 7.4 cases per 100 000 population.

Between September 1989 and August 1993, a physician-based surveillance system for CFS was established in four U.S. metropolitan areas: Atlanta, Georgia; Wichita, Kansas; Grand Rapids, Michigan; and Reno, Nevada.[52] The objectives of this surveillance system were to collect descriptive epidemiologic information from patients who had unexplained chronic fatigue, estimate the prevalence and incidence of CFS in adult populations (greater than or equal to 18 years) and describe the clinical course of CFS. The crude estimates of the 4-year period prevalence of CFS ranged from 3.8 to 9.6 cases per 100 000 population.

Later, the CDC conducted a cross-sectional telephone survey to describe the prevalence and demographic distribution of conditions associated with chronic fatigue in residents of San Francisco, California. Interviews were completed for 16 970 individuals, of whom 4.3% reported chronic fatigue. Having excluded cases with medical or psychiatric diagnoses that could potentially explain fatigue, the investigators identified 1.8% of the population as having idiopathic chronic fatigue and 0.2% as having a CFS-like illness.[53]

To estimate baseline prevalence and 1-year incidence of CFS, CDC researchers conducted a 4-year study in Wichita, Kansas, which has a population with demographic features (e.g., age, sex, race, ethnicity, income) similar to those of the U.S. general population.[54] The overall prevalence of CFS in Wichita was 235 per 100 000 adults (0.23%). The illness was more than four times more common among women (373 per 100 000) than among men (83 per 100 000), and it was most common among white women 50 to 59 years of age (863 per 100 000). The 1-year CFS incidence was 180 per 100 000 persons (0.18%).

Recently, CDC researchers estimated the prevalence of CFS in metropolitan, urban, and rural populations of Georgia, based on a random-digit dialing survey.[55]

This report, focused on the 5 623 of 19 381 respondents aged 18 to 59 years old, estimated that approximately 2.5% of the adult population in Georgia suffered from CFS. There were no significant differences in prevalence of CFS between metropolitan, urban or rural populations or between white and black residents of the three regions. However, there were significant differences in female-to-male ratios of prevalence across the strata (metropolitan female:male=11.2:1, urban=1.7:1, rural=0.8:1).

This proportion is 6- to 10-fold higher than previous estimates of CFS in Wichita and Chicago. Authors believe these estimates are more accurate than previous estimates because they identified unwell adults who were then evaluated for CFS whereas previous studies have screened the population only for fatigue and evaluated fatigued adults for CFS. This is also the first population-based study to diagnose CFS based on a complete clinical and psychiatric evaluation (to rule out exclusionary conditions) and to define disability, fatigue, and accompanying symptoms by means of standardized, internationally validated and reproducible criteria.

Lindal et al. carried out a study to estimate the prevalence of CFS in Iceland[56] using a 95-item custom-made questionnaire sent to 4 000 randomly selected people aged 19-75 year old. The response rate was 63%. The questionnaire was constructed to include questions on all the items found in the four most common criteria for diagnosing CFS; the criteria being Australian, British and American. Results showed very different prevalence estimates according to the criteria used. The prevalence ranged from 0 (CDC-1988) to 4.9% (Australian definition), with the most established criteria yielding a prevalence of 1.4% (CDC-1994).

No prevalence figures are available for Belgium, France, Germany or The United Kingdom. In the Netherlands, no researchers used the CDC-1994 criteria to conduct a community-based study. To estimate CFS prevalence, data from general practitioners based on different definitions were used.[57,58] From these, prevalence was estimated to 110-112 patients per 100 000 inhabitants, i.e. 16 300 patients in the Netherlands. This prevalence is lower than the lowest prevalence estimated in international researches using CDC-1994 criteria (diagnosed by a physician), i.e. 235 per 100 000 (or 38 300 patients in the Netherlands). Consequently, it was estimated that 30 000 to 40 000 of people would be affected by CFS in the Netherlands.[59] This estimation is an extrapolation of research findings obtained in other countries and was not actually verified.

2.4.2 Prevalence of CFS in children

2.4.2.1 Primary care studies

Two studies[23,60] identified cases by local physician surveillance, confirming diagnosis with follow-up interviews or questionnaires. Prevalence estimates were 5.5/100 000 (95% CI 0.1/100 000 - 30.5/ 100 000) in children under 10's and 48/100 000 (95% CI 22/100 000 – 91/100 000) in young people 10-19 year olds in Australia[23] and 2.7/100 000 in 12-17 year olds in the United States although this study used a stricter case definition and only half the eligible physicians participated.[60]

A postal survey of 1 024 GP practices in UK[61] identified 410 cases, 51% of whom had CFS, severe or chronic fatigue as a diagnosis (severe disabling fatigue for at least 3 months with a pre-morbid level of activity significantly reduced or impaired). This study was a retrospective cross-sectional survey with no validation of the diagnostic information or clinical assessment of cases and a broad case definition. Authors showed the prevalence of medically unexplained severe fatigue over three months in 5-19 year olds to be 62/100 000 (95% CI: 56/100 000 – 69/100 000). Cases were predominantly adolescent girls and were more likely to come from practices in less deprived areas, which could reflect consulting behaviours.

2.4.2.2 Community-based studies

In a large cross-sectional study, Chalder et al.[62] determined the prevalence of chronic fatigue syndrome in 4 240 5-15 year old children. Authors compared self reported chronic fatigue (prevalence: 0.57%; 95% CI: 0.34%–0.80%), criteria from the US Centers for Disease Control and Prevention (CDC) for chronic fatigue syndrome (prevalence: 0.19%; 95% CI: 0.06%–0.32%), and parental report of myalgic encephalomyelitis or

chronic fatigue syndrome (prevalence: 0.038%; 95% CI: 0.00%–0.076%). The rates of the syndrome were lower than those found in equivalent surveys in adults.

Farmer et al.[63] used two general population based twin series to derive lifetime prevalence estimates of different definitions of chronic fatigue in 8- to 17-year-olds. Parents completed self-report questionnaires for their children (n = 2 936) that enquired whether either child had ever experienced more than a few days of disabling fatigue. Telephone interviews were undertaken for individuals who had experienced such an episode (96 children). The estimated prevalence of fatiguing illness lasting 3 months or more was 2.34% (95% CI: 1.75% – 2.94%) whereas the prevalence of fatigue lasting 3 months accompanied by at least four minor symptoms from the Centers for Disease Control criteria for CFS was 1.90% (95% CI: 1.40% –2.40%). Lastly, the prevalence of 6 months or more of fatigue with at least four minor symptoms was 1.29% (95% CI: 0.87% – 1.71%).

Jones et al.[64] also tended to estimate the prevalence of CFS (CDC-1994 criteria) in adolescents (aged 12 through 17 years) by a random digit dialing survey of the residents of Wichita, Kansas. Of 8 586 adolescents, 138 had fatigue for ≥1 month and most (107 or 78%) had chronic fatigue (≥6 months) at some point during the 3-year follow-up. The baseline weighted prevalence of CFS-like illness was 338 per 100 000.

A random general population sample of 842 British adolescents (aged 11 through 15 years) was assessed to describe prevalence and incidence of CFS according to CDC criteria.[65] The point prevalence was 0.1% for CFS (95% CI: 0.0% – 0.4%).

Table 1. Prevalence of CFS (and 95% Confidence intervals) according to the age group, the setting and the CFS-definition

Study	Country	N, response rate (%)	Ascertainment	Setting	CDC-1988	CDC-1994	Australian	British	No valid definition
Adults									
Bates, 1993[50]	Massachusetts (USA)	N = 1 000 99%	Self report	Primary care	-	0.3% (0.0-0.6)	1.0% (0.4-1.6)	0.4% (0.0-0.8)	
Wessely, 1997[49]	UK	N = 2 376 83%	Self report	Primary care	0.1% (0.0-0.5)	0.5% (0.1-0.3)	0.2% (0.1-0.5)	0.7% (0.3-1.1)	
Lloyd, 1990[23]	Australia	N = 104 practitioners N = 500 CFS patients	Practitioner report	Community	0.037% point prevalence				
Price, 1992[51]	USA	N = 13 538 75%	Self report	Community	0.007% life-time prevalence				
Reyes, 1997[52]	USA	N = 409 practitioners, 49% N = 565 CFS patients, 87%	Physician surveillance system for CFS	Community	0.0038% to 0.0096% 4-year period prevalence				
Steele, 1998[53]	San Francisco (USA)	N=16 970 87%	Self report	Community	-	0.2%	-	-	
Lindal, 2002[56]	Iceland		Self report	Community	0%	1.4%	4.9%		
Reyes, 2003[54]	Kansas		Physician report	Community	-	0.2%	-	-	
Reeves, 2007[55]	Georgia (USA)	N = 5 623	CDC reports (validated instruments)	Community	-	2.5%	-	-	
Children and adolescents									
Lloyd, 1990[23]	Australia			Primary care	0.005% (<10 years) (0.0001-0.03) 0.048% (10-19 years) (0.022-0.091)				

Study	Country	N, response rate (%)	Ascertainment	Setting	CDC-1988	CDC-1994	Australian	British	No valid definition
					point prevalence				
Dobbins, 1997[60]	USA			Primary care		0.0027% (12-17 years) lifetime prevalence			
Haines, 2005[61]	UK	N = 718 GP practices 70%	GP report	Primary care					0.062% (0.059-0.069)
Chalder, 2003[62]	UK	N = 10 438	Self report CDC definition Parental report	Community		0.19% (5-15 years) (0.06–0.32) point prevalence			Self-report: 0.57% (0.34–0.80) Parental report: 0.038% (0.00–0.076)
Farmer, 2004[63]	South Wales and Greater Manchester (UK)	N = 1 468 65%	Parents report	Community		**fatigue > 3 months** 1.90% (8-17 years) (1.40–2.40) **fatigue > 6 months** 1.29% (0.87-1.71) lifetime prevalence			
Jones, 2004[64]	Wichita, Kansas (USA)			Community		0.338% (12-17 years) point prevalence			
Rimes, 2007[65]	UK	N = 842 77%	Validated instruments Non clinical interviewers	Community		0.1% (11-15 years) (0.0 – 0.4).			

2.4.3 Prevalence: discussion

Epidemiological studies and their estimates differ according to the setting in which they were conducted (e.g. community, primary care, tertiary care); the age of population considered, the definition or criteria used for diagnosis; the instruments used to define CFS and to exclude other medical and/or psychiatric conditions, more or less specific and sensitive; the method of ascertainment (e.g. self-report, parent report, physician report, chart review); the time course of ascertainment (e.g. retrospective, prospective); the sampling method (e.g. random, consecutive, referred, volunteers) and the response rate of the population that is studied.[66]

In general, more restrictive definitions of CFS, excluding psychiatric or other medical diagnoses and requiring longer duration of fatigue lead to lower prevalence estimates compared to less restrictive definitions. For example, use of the 1988 CDC criteria, which are the most stringent, appeared associated with the lowest prevalence estimates. Moreover, community populations have lower prevalence estimates than primary care or hospital populations.[66]

Evidence suggests a population prevalence of at least 0.2-2.5%. Such a prevalence means that a general practice with a population of 10 000 patients is likely to have between 20 and 250 patients with CFS. It is important to underline that the higher prevalence estimated in Georgia reflects a difference in screening criteria. This survey screened for unwell (the core symptoms of CFS) whereas previous studies have only screened for fatigue.[55] This less restrictive approach allowed the inclusion of potential CFS cases omitted with the more exclusive criteria "fatigue".

The 6- to 10-fold greater prevalence estimates also reflect application of more sensitive and specific measures of the CFS diagnostic parameters specified by the 1994 case definition. Previous surveys did not use validated standardized instruments to define CFS but queried as to the presence or absence of fatigue, accompanying symptoms, and impairment. Following the recommendations published by the *International Chronic Fatigue Syndrome Study Group,* Reeves et al. (2007)[55] used validated instruments to obtain standardized measures of the major symptom domains of the illness: 1) the SF-36, to measure functional impairment; 2) the Checklist Individual Strength or MFI, to obtain reproducible quantifiable measures of fatigue; 3) and the CDC Symptom Inventory to document the occurrence, duration and severity of the symptom complex. This results in detecting about 3 times the number of CFS cases as verbatim application of the 1994 definition.

Prevalence estimates also differ according to the period of evaluation: point prevalence, 4-year period prevalence or lifetime prevalence. Because of the long duration of CFS, the period prevalence estimates can be more appropriately compared with the point prevalence estimates.[52]

For adolescent patients (>10 years), prevalence estimates range between 0.0027% and 0.338%. Such estimates mean that a general practice with a population of 10 000 adolescent patients is likely to have between 1 and 34 patients with CFS. For younger patients (5-15 years), prevalence estimates are 0.1% in community, indicating that 10 patients would have the CFS diagnosis in a 10 000 children population.

2.4.4 Incidence of CFS in adults

There are few studies having estimated the incidence of CFS. Their results are summarized in Table 2.

Lawrie et al.[67] estimated that the annual incidence of CFS was 370 per 100 000, but their sample was non-random and relatively small.

During a 4-year surveillance period in four US metropolitan areas, Reyes et al. (1997)[52] identified 19 incident cases. The overall annual incidence rates, as well as the site-specific annual incidence rates, were less than one case per 100 000 persons.

Reyes et al. (2003)[54] conducted a prevalence study in Wichita (0.23%) completed by a 1-year follow-up telephone interview and clinical examination to estimate the incidence of

CFS. Among subjects who were nonfatigued and fatigued for less than 6 months, the 1-year incidence of CFS was 180 per 100 000 persons (95% CI, 0-466 per 100 000 persons).

Results from attempts to estimate incidence in the Netherlands (research team from Nijmegen) indicate that 2 900 to 9 800 new cases could be diagnosed by year, i.e. an incidence of CFS being 18 per 100 000 persons to 60 per 100 000 persons[c].[59]

2.4.5 Incidence of CFS in children and adolescents

A longitudinal study is needed to estimate incidence of CFS. Rimes et al. (2007) conducted such study in a random general population sample of 842 British adolescents (aged 11 through 15 years).[65] At time 1, the point prevalence was 0.1% for CFS (95% CI: 0.0% – 0.4%). Four to six months later, 4 new cases of CFS occurred for a 0.5% incidence (95% CI: 0.01% – 0.9%).

2.4.6 Incidence: discussion

Results from attempts to estimate incidence in adult populations indicate that 1 to 37 new cases could be diagnosed by year per 10 000 population. For adolescents, 100 new cases could be diagnosed by year per 10 000 population. This high incidence is balanced by high remission rates 4 to 6 months later.[65] Overall, taking this high remission rate into account, CFS in children and adolescents may not be extremely disabling. The presence of family psychopathology may be a determining variable, but this deserves further study.

[c] In 2004, number of inhabitants equalled 16.3 million (http://www.cbs.nl/nl-NL/menu/themas/bevolking/publicaties/artikelen/archief/2004/2004-193-pb.htm)

Table 2. Incidence of CFS (and 95% Confidence intervals) according to the age group, the setting and the CFS-definition

Study	Country	N, Response rate (%)	Ascertainment	Setting	CDC-1988	CDC-1994	Australian	British
Adults								
Lawrie, 1997[67]	Scotland (UK)			Community	-	-	-	0.37% (0.4-1.3) 1-year incidence
Reyes, 1997[52]	USA	N=409 practitioners, 49% N=565 CFS patients, 87%	Physician surveillance system for CFS	Community	<0.001% 1-year incidence			
Reyes, 2003[54]	Kansas		Physician report	Community	-	0.18% (0.0-0.5) 1-year incidence	-	-
Children								
Rimes, 2007[65]	UK	N = 842 77%	Validated instruments Non clinical interviewers	Community	-	0.5% (11-15 years) (0.01 – 0.9) 4 to 6 months incidence	-	-

2.4.7 Gender, Social Class, Ethnicity and Geographical Variation

According to CDC[30]:

CFS occurs up to four times more frequently in women than in men, although people of either gender can develop the condition. For children, the evidence for a gender difference in CFS is inconclusive. Whereas a cross-sectional study in UK[62] reported no significant gender difference, another UK study reports a female excess of two thirds to a third[63], as does a US study[60] and the Australian study.[23]

The condition occurs most often in people between the ages of 40 and 59, but people of all ages can get CFS. CFS is less common in children than in adults. Studies suggest that CFS is more prevalent in adolescents than in children.

CFS occurs in all ethnic and racial groups, and in countries around the world. Research indicates that CFS is at least as common among African Americans and Hispanics as it is among Caucasians.

People of all income levels can develop CFS, although there's evidence that it's more common in lower-income than affluent individuals.

CFS is sometimes seen in members of the same family, but there's no evidence that it's contagious. Instead, there may be a familial or genetic propensity. Further research, also including family psychodynamics, is needed to explore this.

Key messages

Prevalence and incidence estimates differ according to:

- **the setting in which they were conducted (e.g. community, primary care, tertiary care);**
- **the age of population considered (adults, children < 10 years old, adolescents from 8 to 19 years old);**
- **the definition or criteria used for diagnosis;**
- **the instruments used to define CFS and to exclude other medical and/or psychiatric conditions, more or less specific and sensitive;**
- **the method of ascertainment (e.g. self-report, parent report, physician report, chart review);**
- **the time course of ascertainment (e.g. retrospective, prospective);**
- **the sampling method (e.g. random, consecutive, referred, volunteers)**
- **the response rate of the population that is studied.**

Prevalence

- **Adults prevalence (1994-CDC criteria)**
- **Self report or GPs (screening "fatigue"): ≤ 1% in primary care; 0.2% - 1.4% in community**
- **CDC reports with validated instruments (broader definition – screening "unwell"): 2.5% in community**
- **Children prevalence (1994-CDC criteria)**
- **Age ranges differ between studies : from 5 to 19 years**
- **Self report, parental report, or GP report: <0.01% in primary care; 0.2% - 1.9% in community**
- **Validated instruments : 0.1% in community**

Incidence

- **Adults incidence :**
- **Large spread (1-4 years) depending on study**
- **very few incidence studies**

- **Children incidence : only one study in adolescents**

More prevalent in women and between 40-59 years old, less frequent in children compared to adolescents in adults

Equally prevalent in all ethnic and racial groups, probably more prevalent in lower income classes

2.5 TREATMENT: A LITERATURE REVIEW

2.5.1 Aims of intervention

To reduce levels of fatigue and associated symptoms, to increase levels of activity and to improve quality of life and neuropsychological performance.

2.5.2 Outcomes measured

Studies typically have assessed severity of symptoms and their effects on physical function and quality of life.

Firstly, studies assessed the level of fatigue, using one or more of the following instruments:

- the 11-item self-report Chalder Fatigue Questionnaire (score range 0-11, where scores ≥ 4 correspond to excessive fatigue).[68]
- the 20-item fatigue subscale of the Checklist Individual Strength (CIS), a Dutch scale with scores ranging from 8 [no fatigue at all] to 56 [maximally fatigued]. The CIS has 4 subscales: fatigue severity, concentration, reduced motivation and, physical activity. The fatigue severity subscale measures both general and physical fatigue and a score above 36 represents severe fatigue. The CIS focuses on fatigue over the preceding two weeks.[69]
- the Krupp Fatigue Severity Scale includes 9 items rated on 7-point scales and is sensitive to different aspects and gradations of fatigue severity. Most items in the Krupp scale are related to behavioural consequences of fatigue.[70]
- the Abbreviated Fatigue Questionnaire, a rating scale of subjective bodily fatigue (score range 4-28, where a lower score indicates a higher degree of fatigue).
- the Multidimensional Fatigue Inventory (MFI), with five subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (each with a score range of 4-20, higher scores indicate higher degree of fatigue); and self-reported severity of symptoms and levels of activity.

There are several instruments used to measure impact of fatigue on disability and quality of life including:

- The Medical Outcomes Survey Short Form-36 (MOS SF-36) is a well-validated instrument that measures the effects of the entire illness (i.e., fatigue and accompanying symptoms) on physical activity, social activity, usual role activities, bodily pain, general mental health, vitality, and general health perceptions (score range 0-100, where 0 = limited in all activities and 100 =able to carry out vigorous activities). Considerable normative data are available for many illnesses including CFS.[28]
- the Karnofsky scale, a modified questionnaire originally developed for the rating of quality of life in people having chemotherapy for malignancy, where 0 = death and 100 = no evidence of disease;
- the Beck Depression Inventory, a checklist for quantifying depressive symptoms (score range 0-63, where a score of ≥ 20 is usually considered clinically significant depression);
- the Hospital Anxiety and Depression scale was designed as a self-assessment instrument for detecting clinically significant depression

and anxiety in patients attending outpatient medical clinics, and for discriminating between anxiety and depression. It has been widely used as a screening instrument outside of the hospital setting, and also for rating psychiatric patients.[71,72,73,74,75,76] The HADS is a patient-completed, 14-item scale, with seven items measuring anxiety (HADS-A) and seven measuring depression (HADS-D). Scores range from 0 to 21 for each scale; higher scores represent more distress. The time frame refers to mood during the past week so as to avoid the influence of possible immediate changes, such as those due to the stress of attending the clinic appointment. The HADS has good psychometric properties. Cronbach alpha was reported in 15 studies and varies for HADS-A from 0.68 to 0.93, and for HADS-D from 0.67 to 0.90. The two factor structure corresponding to anxiety and depression is confirmed in literature. The HADS discriminates well between samples with high, medium, and low prevalence of anxiety or depressive disorders. It allows longitudinal assessments with repeated testing at intervals of about 1 week or more and is sensitive to change in patients' emotional state.

- The Sickness Impact Profile (SIP) measures functional disability in different areas of daily functioning. Eight subscales of the 12 available are generally used in CFS: alertness behaviour, sleep, homemaking, leisure activities, work, mobility, social interactions, and ambulation. Like the MOS SF-36, the SIP measures the consequences of the entire illness. However, the SIP records disability in concrete activities, which makes it less dependent on subjective impression.[77]
- the Clinical Global Impression scale, a validated measure of overall change compared with baseline at study onset (7 possible scores from \"very much worse\" [score 7] to \"very much better\" [score 1]); the original CGI is a simple instrument rating the overall severity of a mental disorder.
- the Nottingham Health Profile, with questions in six self report categories: energy, pain perception, sleep patterns, sense of social isolation, emotional reactions, and physical mobility (maximum weighted score 100 [all listed complaints present], and minimum 0 [none of listed complaints present]);

Some of these questionnaires are presented in Appendix 6.

Objective measures used in some studies include absenteeism from work or school, exertion tests, physical outcome measures [incremental shuttle walk test (ISWT)] and tests of cognitive functioning such as attention, reaction time, and short-term memory.

2.5.3 Therapeutic strategies

Many interventions have been tried for the treatment, management and rehabilitation of patients with CFS from prolonged rests to drug therapies and dietary supplements. However, treatments most reported in published outcome studies are cognitive behavioural therapy including cognitive restructuring, building up activity, returning to work and relapse prevention[78,18] and graded exercise therapy.[79,80,81,82,83]

Bagnall et al. (2007)[1] completed the most recent review of CFS treatment efficacy, including 70 trials (CRD Report 35). Of the studies included in the review, 59 were RCTs and the remainder non-randomised controlled trials. Validity assessment of each study was carried out by two reviewers from CRD using predefined criteria (randomisation, concealment of allocation, participant blinding, investigator blinding, baseline comparability of groups, follow-up, intention to treat, outcome objectivity, quality of statistical analysis, sample-size calculation and comparability of treatment of groups). The evaluation scale ranged from 0 (poor validity) to 20 (high level of validity). Scores ranged from 2 to 19 for the included RCTs and from 0 to 14 for the controlled trials. Controlled trials generally scored less well than RCTs on all validity criteria. A high degree of heterogeneity in interventions (as well as in outcomes) was evident.

These trials investigated the effectiveness of seven different categories of intervention: behavioural, immunological, antiviral, pharmacological, supplements, complementary/ alternative and other.

Our search strategy identified more recent RCTs published after the literature review conducted by Bagnall et al. These RCTs were included in this report. For critical appraisal of these studies, see Appendix 7. All studies considered are presented in Appendix 8.

2.5.3.1 Cognitive behavioural therapy (CBT)

Cognitive behavioural therapy is an evidence-based psychological therapy that is used in many health settings, including cardiac rehabilitation and diabetes management. CBT is a combination of cognitive and behaviour therapy. Cognitive therapy is based on the idea that certain ways of thinking can 'fuel' certain health problems. Behaviour therapy aims to change any behaviour that is harmful or not helpful. CBT aims to reduce the severity of symptoms (by improving coping strategies and day-to-day functioning) and if possible to 'cure' the condition. The aim is to get CFS patients to think differently about their illness, and its symptoms. In practical terms it involves getting patients to consider other attributional causes for their fatigue and distress, illness attribution having a profound effect on disability.[84] The use of CBT does not assume or imply that symptoms are psychological or 'made up'.

For people with CFS the core components of CBT would normally include: energy/activity management, establishment of a sleep routine, goal setting, and psychological support.

In the CRD report[1], CBT was evaluated in adults in five RCTs[85,86,87,88,89] and in adolescents in one RCT.[90]

Beyond the RCTs included in this systematic review, we found more recent papers respecting our inclusion criteria. One RCT was conducted in an outpatient group program.[91] One recent study[92] combined results obtained in two previous RCTs either in adult population[93] or in adolescent population[90] aiming to evaluate cognitive impairment and neuropsychological performance. One controlled trial was also conducted among an adolescent population using CBT combined with biofeedback.[94]

All studies included people diagnosed with CFS according to one of the recognised case definitions (Australian definition, Oxford definition or 1994-CDC criteria). The sample size ranged from 60 patients[86] to 278 patients.[88]

CBT was compared to:

- routine medical care (assessment, advice, and follow up in general practice) in four RCTs[86,89,94,91]
- relaxation (progressive muscle relaxation and rapid relaxation) in one RCT[87] and its 5 year follow up[95]
- natural course (control) in two adult RCTs[88,93] and in one adolescent[90]
- guided support in three RCTs[88,93, 91]
- immunological therapy (dialysable leucocyte extract, DLE), with four treatment arms: CBT plus DLE; CBT plus placebo (saline); standard care plus DLE; and standard care plus placebo (saline)[85]

MAIN RESULTS FOR CBT

One RCT used a brief-CBT which consisted of patient information booklet (explanatory models of CFS), recording levels of activity and encouraging gradual increase at appropriate level and rate to usual care. This information was completed by a discussion of beliefs and behaviours around CFS. This treatment was compared to usual care including referral to secondary care. No significant differences were reported between the groups in terms of fatigue, disability, anxiety and depression.[89]

The RCT which investigated the effects of both leukocyte extract and CBT showed a significantly greater effect on general health in the group receiving both leukocyte extract and CBT compared to the other groups ($p<0.05$).

No differences were found between groups (including CBT alone) for the other outcomes investigated (physical capacity and functional measures, mood or immune outcomes [CD4, CD8 cell counts and DTH skin response], quality of life measures. Authors conclude that neither dialyzable leukocyte extract nor CBT (alone or in combination) provided overall greater benefit than the non specific treatment regimens.[85]

The RCTs which compared CBT to no treatment either in adult population[88], either in adolescent population[90] found that CBT significantly reduced fatigue severity and functional impairment. Among adolescent, the RCT also found that CBT significantly improved school attendance.[90]

In 2007, Knoop et al.[92], using previous RCTs data,[90,93] showed that CBT also significantly reduced concentration disturbances in adults and adolescents but had no effect on neuropsychological performance (e.g. reaction time and complex attention).

The remaining four RCTs reported a beneficial effect of CBT when compared to other treatments, such as relaxation,[87] normal general practice care,[86,91] guiding support.[88,91] All four RCTs found a significant short term improvement (6-12 months) in physical functioning, fatigue, and global improvement, but neither of the two studies that assessed depression found any differences between groups.[87,86] A higher proportion of CBT patients falls within the normal range for physical scores at 12 months follow-up with a significant improvement in walking speed.[91] One of these RCTs also followed patients for five years after the intervention. Fifty-three patients (88%) of the original study participated in the follow-up study: Among them, 25 received cognitive behaviour therapy and 28 received relaxation therapy. At the five year follow-up assessment,[95] global improvement was significantly greater in the CBT group. Significantly more patients receiving CBT in relation to those in relaxation therapy, met criteria for complete recovery (patients no longer met UK criteria for CFS, employed full-time, and scored less than 4 on the Fatigue Questionnaire and more than 83 on the MOS SF-36 physical functioning scale), i.e. 24% v 4% (p=0.04); were free of relapse, i.e. 36% v 7% (p=0.02); and experienced symptoms that had steadily improved or were consistently mild or absent since treatment ended, i.e. 68% v 43% (p=0.05). Similar proportions were employed, i.e. 56% v 39% (p=0.28), but employed patients in the CBT group worked significantly more mean hours per week, i.e. 35.57 (SD=8.11) v 24 (SD=4.97) (p<0.04). However, authors explain that more relaxation therapy patients than CBT patients participated in the follow-up study (3 CBT patients had a newly diagnosed medical condition that might have contributed to chronic fatigue, and 6 relaxation therapy patients received CBT after the end of the original trial).[95]

In a controlled trial, Al-Haggar et al.[94] combined successfully CBT with biofeedback in CFS adolescents. Biofeedback is a treatment technique in which people are trained to improve their health by using signals from their own bodies. Physical therapists use biofeedback to help stroke victims regain movement in paralyzed muscles. Psychologists use it to help tense and anxious clients learn to relax. Specialists in many different fields use biofeedback to help their patients cope with pain.[94] This combined therapy showed statistically significant improvements in self-rated CFS symptoms (fatigue, headache and myalgia showed) (p<0.01) whereas joint pains and tender glands did not significantly improved. This treatment also improved school attendance.

There are very few studies which reported how many patients would require CBT to reduce the expected number of cases of a defined endpoint by one, i.e. number needed to treat (NNT) (see Table 3). Two high quality level RCTs in adults report this information.[86,87] The RCT conducted by Sharpe[86] compared CBT versus normal general practice care in people attending a secondary care centre. Results showed that CBT significantly improved quality of life (Karnofsky scale) at 12 months compared with standard medical care (final score > 80: 22/30 [73%] with CBT v 8/30 [27%] with placebo; RR 2.75, 95% CI 1.54 to 5.32; NNT 3, 95% CI 2 to 5). The RCT conducted by Deale[87] compared CBT with relaxation therapy. It found that CBT significantly improved physical functioning compared with relaxation therapy (improvement based on predefined absolute or relative increases in the SF-36 score: 19/30 [63%] with CBT v 5/30 [17%] with relaxation; RR 3.70, 95% CI 2.37 to 6.31; NNT 3, 95% CI 1 to 7). Results are at 6-month follow-up but improvements were sustained over 6 months of follow-up.

At the five year follow-up assessment[95] global improvement was greater in the intervention group (17/25 [68%] with CBT v 10/28 [36%] with relaxation therapy; RR 1.9, 95% CI 1.1 to 3.4; NNT 4, 95% CI 2 to 19).

The RCT conducted in children,[90] comparing CBT versus no intervention, reports sufficient information to calculate NNT. The RCT found that CBT significantly reduced fatigue severity (change in Checklist Individual Strength score at 5 months: -22.3 with CBT v -7.6 with no intervention, difference 14.5, 95% CI 7.4 to 21.6; NNT=3) and functional impairment compared with no treatment (change in SF-36 score at 5 months: 27.3 with CBT v 10.0 with no treatment, difference 17.3, 95% CI 6.2 to 28.4; NNT=3). The RCT also found that CBT significantly improved school attendance (change in percentage school attendance at 5 months: 28.5% with CBT v 10.3% with no treatment; difference 18.2%, 95% CI 0.8% to 35.5%, NNT=3).

Table 3. Number needed to treat by CBT

Study	Population	Treatment strategies	Outcomes	NNT
Sharpe (1996)[86]	Adults	CBT v normal general practice care	Quality of life at 12 months	3
Deale (1997)[87]	Adults	CBT v relaxation therapy	Physical functioning at 6 months	3
Deale (2001) [95]	Adults	CBT v relaxation therapy	Global improvement at 5 years	4
Stulemeijer (2005)[90]	Children	CBT v no intervention	Fatigue severity, functional impairment and school attendance at 5 months	3

MAIN RESULTS FOR MODIFIED COGNITIVE BEHAVIOURAL THERAPY (MCBT)

The CRD systematic review[1] envisaged 5 studies using a modified cognitive behaviour therapy, four in adults (3 CCTs and 1 RCT) and one in children (1 CCT). The "modified CBT" covers different modalities in treatment. One CCT[96] of low quality evidence envisaged a CBT which did not include graded activity (normally considered an integral part of CBT for CFS), but focused on shared coping through relaxation training and guided imagery, cognitive therapy techniques and behavioural prescription involving activity limitations. This controlled trial of modified CBT found no difference between intervention and control groups for fatigue, depression or symptom scores. This study scored very poorly on the validity assessment, scoring only 1 out of a possible 20; so results have to be interpreted with caution.

Other types of modified CBT, with occupational therapy/rehabilitation aspects, were examined in one RCT[97] of high quality evidence and two controlled trials in adults[98,99] of low quality evidence. These three studies found significant differences between groups for symptoms (one RCT, one controlled trial), emotional distress (one controlled trial) and global health/ quality of life (3 controlled trials). In children, one CCT[100] of moderate quality evidence found significant difference in favour of treatment group in term of school attendance and severity of the condition (complete resolution of CFS: 43% with CBT v 4.5% with supportive care; difference 38.5%, NNT=3).

DIFFERENCES IN CBT CONTENT AND MODALITIES OF TREATMENT

The treatment offered to patients receiving a particular type of therapy in practice may vary considerably, particularly for behavioural interventions. For example, in the high quality study conducted by Lloyd (evidence quality 1A),[85] CBT was given every 2 weeks for six sessions of 30-60 minutes each, and people were encouraged to exercise at home and feel less helpless. In the high quality study by Sharpe (evidence quality 1A),[86] patients were offered a cognitive behavioural assessment, followed by 16 weekly sessions of behavioural experiments, problem solving activity, and re-evaluation of thoughts and beliefs that inhibited a return to normal functioning.

In Prins' study (evidence quality 1A),[88] the CBT consisted of 16 sessions over 8 months administered by 13 therapists with no previous experience of treating CFS.

In the CBT study by Stulemeijer et al. (evidence quality 1B),[90] participants in the intervention group received ten individual therapy sessions over 5 months in a hospital child psychology department, whereas in the RCT conducted by Whitehead et al. (evidence quality 1B),[89] the intervention was a form of 'brief CBT' delivered by general practitioners. This brief-CBT consisted of patient information booklet (explanatory models of CFS), recording levels of activity and encouraging gradual increase at appropriate level and rate. This information was completed by a discussion of beliefs and behaviours around CFS. The use of a brief-CBT did not lead to significant differences in favour of treatment group.

One of the major differences in treatment modalities concerned the therapeutic format, i.e. individual therapy or group therapy. All studies reported in the CRD Report 35 used an individual CBT. In 2005, Bazelmans et al. (2005)[101] published a non-randomised waiting list controlled study about effectiveness of group therapy (evidence quality 2B). Authors found that group CBT was effective on daily observed fatigue. However, no positive results were obtained for CIS fatigue or for functional impairment, compared to studies using individual therapies. Explanations for this low effect included CBT format and inexperience of therapists, both in group therapy and in CBT for CFS. Also, the non-randomisation of this study might have induced biases as to patient selection.

Later, O'Dowd et al. conducted a RCT in which CBT was delivered in patient' groups (evidence quality 1B).[91] There were significant improvements in the CBT group in the measures used for fatigue, mental health and walking speed. The treatment did not, therefore, restore 'normal' levels of physical function on the SF-36. This result was comparable to the changes seen in the individual research literature. Group CBT did not significantly improve cognitive function, quality of life (as measured by the physical subscale of the SF-36) or employment status while such changes have been demonstrated in the literature for individual CBTs.[91]

Bazelmans et al. (2005) summarized the advantages and disadvantages of group therapy.[101] Advantages include the opportunity to treat simultaneously a higher number of patients and the modelling process which could facilitate behavioural change. Disadvantages include the opportunity for CFS patients to reinforce dysfunctional behaviour and resistance against psychological treatment; moreover, it is also more difficult for patients to individualise CBT treatment to individual needs. Further evaluation of methods for delivering behavioural interventions in research and practice would be desirable in order to define the optimal treatment-response (outcome) ratio.

DIFFERENCES IN SETTINGS

The effectiveness of CBT for CFS outside of specialist settings has been questioned.

Supposing that CBT outcomes could be different according to the setting, Qarmby et al.[102] conducted a study to compare outcomes of CBT for CFS within and outside an RCT (evidence quality 1A). The two interventions were carried out within the same clinical setting. Analysis showed superior results in RCT compared to those in routine clinical practice. Between pre-treatment and 6-month follow-up, the RCT showed a larger reduction in fatigue and greater improvement in social adjustment than those in routine treatment. The changes in fatigue scores were similar for both groups during treatment but were greater in the RCT between post-treatment and follow-up.

Potential reasons for the superior results of the RCT include:

- the stricter selection procedure in RCTs and the exclusion of patients with comorbidities (anxiety, depression, …); the application of restrictive exclusion criteria may under represent the more varied referrals to routine care and may limit the generalisability of treatments tested in RCTs;
- the use by trial clinicians of a thoroughly researched protocol that is manualised to ensure replicability across time and therapist; the clinic therapists tend to rely upon their own training and experience when carrying out an intervention, are less strict and focused in routine clinical practice;
- the motivation and supervision of therapists in RCTs;

- the follow-up bias: in RCTs, more patients completed follow-up measures.

The results of the multicentre RCT (evidence quality 1A)[88] suggest that CBT may be effective when administered in an outpatient clinic by less experienced therapists with adequate supervision. However, improvement in this study was lower than in other CBT trials. This lower result is partly explained by the lack of clinical experience of therapists, who recognized the higher difficulty to treat CFS patients compared to patients with psychiatric diagnoses or patients with other functional somatic syndromes. Nevertheless, results are promising and authors recommend transferring CBT outside university medical settings in order to increase accessibility of this treatment for all CFS patients in future.

DIFFERENCES IN OUTCOMES AND FOLLOW-UP

The wide variety of outcome measures used in the included studies makes it difficult to compare the effects of interventions across studies. Even when studies evaluated the same outcome, they used a variety of scales and measures to do so. Researchers failed to provide detailed information about the treatment (e.g. number of sessions) and to provide an effect size for each outcome variable. This heterogeneity and the lack of useful information made it impossible to combine studies by meta-analysis. There also remains a lack of long-term follow-up data for most interventions, although a 5-year follow-up of the RCT of CBT by Deale and colleagues (evidence quality 1A) showed maintained benefit of the intervention for several outcomes.[95] Cognitive behavioural therapy was evaluated positively, and most patients still used the treatment techniques 5 years later. However, once therapist contact ended at 6 months after treatment, some patients had difficulty to progress without support and may have become vulnerable to relapse. Authors recommended that more attention could be paid to ensuring that gains are better maintained over time. For example, regular follow-up sessions at widely spaced intervals for several years after treatment could help patients make a successful phased return to work and achieve lasting lifestyle changes.[95]

EFFICACY OF CBT FOR CFS PATIENTS: META-ANALYSES

The systematic review conducted by Bagnall et al. (2007)[1] concluded that cognitive behavioural treatments, including encouragement of gradual increases in activity, produced promising results. However, this review did not meta-analyze the findings and could not quantify the overall effect size nor examine possible moderators.

In their meta-analysis, Malouff et al.[18] aimed to determine the efficacy of cognitive behavioural treatment for chronic fatigue syndrome and to search for moderators of effect size. This meta-analysis included 13 studies and 1 371 participants. Nine of these studies were individually analyzed in the CRD Report 35.[87,79,83,81,88,86,90,82,80] Treatments used in these 13 studies, although all cognitive behavioural, varied widely in intensity (from 0.2 hours in 1 session to 15 hours in 13 sessions) and specific therapeutic methods (activity with or without cognitive treatment; individual treatment or group treatment). Across analyses, there was a significant difference, d=0.48, in post-treatment fatigue between participants receiving CBT and control groups. The present meta-analytic findings quantify and support reviews and RCTs that have concluded that CBT was useful for CFS patients. However, results also indicate that CBT was "moderately" efficacious while this treatment did not help every CFS patient cease to meet diagnostic criteria. In the five studies[86,90,91,103,104] that reported the number of CBT clients who were no longer in the clinical range with regard to fatigue at the latest follow-up, the percentage varied from 33%[103] to 73%[86] of those assigned to CBT, with a mean of 50%. Three other studies reported the number of CBT clients who showed a large improvement at the time of the latest follow-up or were in or near the normal range. Prins et al. (2001)[88] reported 30%; Deale et al. (1997)[87] reported 63% and Powell et al. (2001)[81] reported 68%. The unweighted average across these three studies was 54%. Dropout rates in CBT varied from 0–42%, with a mean of 16%.

The larger effect size for physical fatigue might be due to the inclusion in each experimental treatment of prompting gradual increases in physical activity whereas no study did include an increase in mental activity (e.g. reading, solving anagrams and crossword puzzles, playing cards, board games, and computer games).

The search for moderators of effect size produced only non significant trends. For instance, the following moderators had no impact on effect size:

- criteria used to diagnose CFS (Oxford or 1994 CDC-criteria),
- restrictive inclusion of individuals diagnosed with CFS (fatigue that had lasted longer is *not* harder to treat),
- type of control group (supervised stretching and client centred treatment *versus* no treatment or usual care),
- inclusion of cognitive components in treatment of fatigue,
- number of treatment hours,
- number of sessions,
- objective and subjective measures,
- individual and group treatment (but only one study dealing with group treatment had been included[91])
- length of follow-up (while slight trend in favour of longer follow-up)

Cho, Hotopf, and Wessely (2005)[19] also used meta-analysis to examine the placebo effect in treatment of CFS and found that the placebo response in CFS treatment was low. The placebo response across studies was less than for some other medical disorders and was lower for psychological interventions than for drug treatment. In other words, little of the effect of CBT for chronic syndrome is due to placebo. The authors recommend more focus on the non-specific, contextual aspects of CFS treatment in order to increase the effect of an active treatment. The collaborative therapeutic relationship was suggested as a key factor in the management of the condition.

- **Cognitive behavioural therapy is effective in adults and has been shown to reduce symptoms, improve function and improve quality of life (Evidence quality 1A) whatever the number of hours, the number of sessions or the treatment format (individual or group);**
- **Evidence available in children indicates that cognitive behavioural therapy is effective in improving fatigue and symptoms, physical function, severity of condition and school attendance (Evidence quality 1A).**

2.5.3.2 Graded exercise therapy (GET)

Graded exercise is a rehabilitative approach based on the principle that prolonged inactivity causes physical deconditioning of the muscles, heart and lungs, which then maintains the effects of CFS. Graded exercise programmes consist of structured supervised activities or exercises that are progressively increased by a therapist in order to improve a patient's physical condition.

Five large RCTs[79,80,81,82,83] considering graded exercise therapy as potential treatment for CFS patients were included both in a Cochrane systematic review[105] and the CRD systematic review.[1]

The following treatment comparisons were made;

- Exercise therapy versus treatment as usual or relaxation (to listen to a relaxation tape and other relaxation techniques) + flexibility (selected stretching exercises but avoiding doing any extra physical activities; maximum 30 minutes daily, 5 days/week),
- Exercise therapy versus pharmacotherapy (fluoxetine),
- Exercise therapy alone versus exercise therapy + pharmacotherapy (fluoxetine),
- Exercise therapy alone versus exercise therapy + patient education.

The exercise therapy regime lasted 12 weeks in all five studies and all used aerobic graded exercise therapy but with mixed levels in terms of intensity, 40% VO_2 maximum to 70% VO_2 maximum, and between 3 to 5 sessions/week with target duration of 30 minutes per session.

Contact with the therapist was minimal, usually once a week and most of the studies used exercise logs to measure adherence to treatment. The control interventions used were treatment as usual, relaxation/ flexibility, pharmacotherapy and patient education.

All RCTs found significant improvements in the intervention group compared to the control groups. Fatigue, as measured by the Chalder fatigue scale, was improved at three months by exercise therapy when compared to the control group (relaxation/ flexibility or treatment as usual).[79] Measures of health-related quality of life and functional work capacity showed benefit of graded exercise over control.

Giving the antidepressant fluoxetine alone is less effective than graded exercise to reduce fatigue. Combining the two interventions, exercise and fluoxetine, significantly reduced fatigue at 26 weeks compared with general advice with or without fluoxetine (Chalder fatigue score< 4:12/67 [18%] with GET v 4/69 [6%] with general advice; RR 3.10, 95% CI 1.05 to 9.10; NNT 9, 95% CI 5 to 91). Further studies are needed to examine this.

An intensive patient educational intervention added to exercise therapy delivered no added benefit when compared to exercise therapy with usual explanation. This has an implication for the feasibility of the intervention, as it does not require large amounts of professional time in order to be effective.

Edmonds[105] concluded that some patients may benefit from exercise therapy. Moreover, there is no evidence that exercise therapy may worsen outcomes. Authors underline that this treatment may be less acceptable to patients than other management approaches, such as rest or pacing.

METHODOLOGICAL ISSUES AND CLINICAL IMPLICATIONS

As for CBT, most studies on GET do not include an objective measure of activity and it is therefore unclear if any of the improvements can be attributed to the exercise regime. The often cited study on GET by Fulcher & White (1997)[79] revealed a significant reduction in mean levels of fatigue and an increase in physical functioning, but none of these measures had returned to normal and there were no improvements for anxiety, depression and quality of sleep. Moreover, there were no data showing that people had increased their activity levels after treatment. In another British study, Wearden et al. (1998)[80] showed a reduction in fatigue and improvement in functional work capacity in patients who completed the programme. However, 37% of the patients dropped out, and again, there was no information on post-trial activity levels.

Moreover, studies on GET conducted in clinical settings have reported less impressive outcomes than the published randomised controlled trials, highlighting the need to evaluate all interventions in routine practice, as well as research clinics (e.g. Quarmby et al. (2007)[102]).

Five trials investigating incremental physical exercise programmes showed improvements in adults in various health outcomes including mental and physical fatigue, global improvement, disability, sleep, mood and cognition (Evidence quality 1A)

Summary of results for CBT and GET

Effectiveness of CBT

- **CBT is effective on physical functioning (functional status, fatigue, pain), psychological state (depression, mood, anxiety, well-being; concentration disturbances in adults and adolescents), quality of life and general health (work and social adjustment, long term goals, global improvement);**
- **CBT is not effective for all patients. It aims at reducing severity of symptoms, and if possible, to cure CFS patients.**

Modalities of treatments

- **Effectiveness of group's therapy: only 1 good quality level RCT (evidence quality 1B) and a lower quality non-randomised waiting list controlled study (evidence quality 2B) were conducted, suggesting that group's therapy was effective; however, the effectiveness was less effective than individual therapy to improve cognitive function, quality of life or employment status. More high quality trials are needed to recommend group therapy;**
- **Modified CBT: mainly studies of lower quality evidence were conducted to assess the effectiveness of modified CBT in CFS patients. Only 1 high quality RCT found positive results for symptoms. A brief-CBT administered by GPs in a RCT of good quality level found no significant results in favour of the treatment group;**
- **Primary care versus secondary care: only 1 RCT of high quality focused on CBT administered in an outpatient clinic by trained therapists (but non-experienced with CFS patients); results were positive but the improvement was lower than in other trials when therapy was performed by highly trained and skilled therapists.**

Effectiveness of GET

- **GET is effective on fatigue, health-related quality of life and perceived functional capacity (questionnaire);**
- **GET is not effective for all patients, and does not improve anxiety, depression and quality of sleep; there is no evidence that GET improves activity levels;**
- **There is no evidence that GET may worsen outcomes.**

Combining CBT and GET

- **No study investigated the added value of the combination of these therapeutic strategies. There is no evidence that this combination could lead to a higher improvement in CFS symptoms. Combining these therapies should take into account incremental costs compared to incremental effectiveness (see chapter 3 on economic evaluation).**

Therapists

- **CBT and GET have to be performed by trained therapists having an experience with CFS patients (1 RCT and 1 non randomised waiting list study);**
- **These therapies should be adapted to the patient's age (particularly for children younger than 12 years), the severity of their CFS, their preferences and experiences, and the outcome of previous treatment(s);**
- **Therapy manuals having proved their validity in scientific studies have to be available.**

2.5.3.3 *Immunological, antiviral and anti-microbial treatments*

Numerous studies have investigated the role of infections in the pathogenesis of CFS and various viruses and virus groups have been implicated in CFS at some time; these include Epstein-Barr virus (EBV), cytomegalovirus, parvovirus B19, *Brucellae, Toxoplasma gondii, C. burnetii, C. pneumoniae*, human herpes virus-6 (HHV-6), group B coxsackieviruses (CVB), human T cell leukaemia virus II-like virus, spumavirus, hepatitis C virus, human lentiviruses and herpes virus-7.[106] The possibility that CFS is associated with an infection has been established.[107,108]

In their systematic review, Bagnall et al.[1] included RCTs which investigated the effects of different immunological or antiviral treatments on CFS patients: antihistamine (oral Terfenadine[109]), antiviral (Acyclovir,[110] Gancyclovir,[111] Inosine Pranobex[112]), immuno-modulators (Immunoglobulin,[113-115] Interferon,[116] Alpha Interferon,[117] leucocyte extract,[85] Ampligen[118]) and vaccine (Staphylococcus toxoid[119,120]).

The RCT which evaluated the antihistamine (oral Terfenadine) found no differences between the groups for any of the outcomes investigated (functional status and symptoms).

Only small RCTs (n<30) evaluated the effect of antiviral treatments on CFS patients. Acyclovir had a significant negative effect on anxiety, depression and confusion in CFS patients who had prior infection with Epstein Barr virus. However, this treatment was ineffective for the other outcomes investigated (rest, anger, vigour, fatigue, oral temperature and personal well-being). Gancyclovir found no beneficial effects. Inosine pranobex found significant improvements in immune function in the treatment group but no differences between groups for other outcomes (symptoms, cognitive function, global severity, activity). Antiviral treatment should be avoided according to the lack of beneficial effects and the presence of adverse effects such as reversible renal failure with Acyclovir, pericardial bleeding during invasive investigations with Gancyclovir and elevation of serum uric acid with Inosine pranobex.

The beneficial effect of Immunoglogulin for CFS patients is controversial. Three RCTs investigated this treatment and obtained mixed results: one found improvements in symptom scores and functional capacity; a second found improvements in immune measurements but not functional or symptom measures, and the third, which was the larger one (n=99) found no effect of treatment. Finally, immunological treatments with Immunoglobulin had more adverse effects (transient abnormal liver function tests, phlebitis, headaches and severe constitutional reaction to infusion were reported) than beneficial effects and should be avoided. One RCT investigated the effect of Immunoglobulin G in adolescents with significant improvements in functional outcome at 6 months.

Other immunomodulators (Interferon, Alpha Interferon, leucocyte extract, Ampligen) were investigated in four RCTs. One study of interferon showed an increase in physical activity (p value not provided) and another showed improvements only in immune measurements but not in quality of life measures. Use of Ampligen showed an improvement in functional ability and cognitive function but not in depression scores. The combination of leukocyte extract and CBT appeared to improve general health in one study (n=49 patients), but not physical or functional capacity, mood or immune outcomes. However, risks are greater than benefits linked to the use of blood products (possible transfer of infectious diseases).

The effects of vaccination with staphylococcus toxoid were investigated in one small controlled trial of patients with CFS (n=28) and one fairly large RCT (n=98). While there was low evidence of benefit for vaccination with staphylococcus toxoid treatment (only for 'the clinical global impression'), the dropout rate was higher in the treatment group according to side effects (local reaction and risk for anaphylaxis).

The systematic review conducted by Bagnall et al. (2007)[1] did not include studies examining the effectiveness of antibiotics in CFS patients. Consequently, we conducted a specific literature search in Medline (OVID) combining 'anti-bacterial agents OR infection' AND 'chronic fatigue syndrome' (April 23, 2008).

Among 44 papers obtained with this key terms, only three papers focused on our objective and were retrieved;[d] the first one investigated the effect of tetracycline antibiotics (minocycline, doxycycline or levofloxacin) for *Coxiella burnetii* in CFS patients;[121] the second one examined the effect of Azithromycin in CFS patients;[122] the third one was a review about Mycoplasma blood infection in chronic fatigue and fibromyalgia syndromes.[123]

Iwakami et al. (2005)[121] treated 4 CFS patients and 54 controls [the post-Q fever fatigue syndrome (QFS) group] positive for *Coxiella burnetii* mainly with minocycline or doxycycline (100 mg/d) for 3 months. After this treatment, all 58 patients tested negative for *Coxiella burnetii* infection. However, the CFS group achieved no improvement in clinical signs and symptoms such as severity of general fatigue, low-grade fever, headache, arthralgia, myalgia and lymphadenopathy after 3 months of treatment. Authors concluded that eradication of *Coxiella burnetii* did not lead to symptomatic improvement. This study is a pilot study (Evidence quality 1C) conducted among a very little sample of CFS patients and further larger investigations are needed to confirm these preliminary results.

Vermeulen and Scholte (2006)[122] conducted a retrospective study in order to evaluate the response of CFS patients to Azithromycin, an antibiotic and immunomodulating drug. They tested this treatment when the effect of counselling and L-carnitine was considered insufficient by the patient and the clinician. The selection of Azithromycin was not based on symptoms or laboratory indications of immune activity. Ninety-nine patients received Azithromycin 500 mg on 3 consecutive days of the week during 6 weeks. Because questionnaires for disease specific symptoms were not available at the treatment period, authors only presented an overall impression of improvement, reported by 58 patients (59%). Lower plasma acetylcarnitine was observed in CFS patients who responded to Azithromycin. No responder fully recovered from CFS by Azithromycin. This study is of very low quality (Evidence quality 2C) and its results are inconclusive.

A third paper focused on mycoplasma infection in chronic fatigue and fibromyalgia syndromes.[123] According to the author, studies using polymerase chain reaction methods showed that mycoplasma blood infection was detected in about 50% of patients with CFS and/or fibromyalgia, including patients with Gulf war illnesses. However, no results were reported to confirm the effectiveness of long-term therapy (up to 1 year therapy) with doxycycline in studies reviewed.

Beside the inconclusive effects of antibiotics in chronic fatigue syndrome, adverse effects of such treatments have to be stressed. Doxycycline and Azythromycin may cause side effects such nausea, vomiting, diarrhea, increased sensitivity of the skin to sunlight and vaginal yeast infection. Some possible uncommon but serious side effects of doxycycline include: a life-threatening allergic reaction, blood problems, liver damage and irritation of the oesophagus (US Food and Drug Administration, 2001; see http://www.fda.gov/cder/drug/infopage/penG_doxy/QA_doxy.htm). In previous studies comparing use of azithromycin and doxycycline for other pathologies (rosacea), diarrhea was reported as a side-effect, which led to discontinuation of the treatment.[124,125]

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[d] A fourth study evaluated benefits and harms of Doxycycline treatment for *Mycoplasma* species in Gulf War Veterans presenting the Gulf War syndrome.[110] This patient group is somewhat similar to CFS patients, in terms of symptoms presented. This study is a high quality RCT comparing patients receiving antibiotherapy (doxycycline 200 mg/d for 12 months) and patients receiving placebo (identically matched lactose capsules). No statistically significant differences were found between the doxycycline and placebo groups for the primary outcome (improvement in physical health functioning) or for secondary outcomes (pain, fatigue, cognitive symptoms and mental health function) at 1 year. Participants in the doxycycline group had a higher incidence of nausea and photosensitivity. The percentage of patients whose blood remained positive for *Mycoplasma* species by polymerase chain reaction testing decreased throughout the treatment period in both treatment groups. Authors conclude that long-term treatment with doxycycline did not improve outcomes of patients with Gulf war syndrome at 1 year.

Moreover, studies have documented an association between macrolide use and the emergence of macrolide-resistant *Streptococcus pneumoniae* and other pathogens, such as *S. pyogenes*.[126,127] According to Bergman et al. (2006),[126] total macrolide use and azithromycin use being associated with increased macrolide resistance, unnecessary prescribing of macrolides should be avoided.

The evidence shows that immunoglobulin therapy in adults with CFS is not of benefit (Evidence quality 1A).

There is insufficient evidence of benefit of other immunological therapies (Evidence quality 1B).

Results obtained in studies examining the effectiveness of antibiotics in adults with CFS are inconclusive (Evidence quality 1C / 2C) and possible side-effects including resistance to antibiotics should be kept in mind.

2.5.3.4 Pharmacological treatments

The pharmacological studies reviewed in CRD report 35[1] included treatment with anticholinergic agents (Sulbutiamine and Galantamine hydrobromide), antidepressants (Phenelzine and Fluoxetine), hormonal agents (growth hormone and melatonin), monoamine oxidase inhibitors (Moclobemide and Selegiline), NADH (nicotinamide adenine dinucleotide), dexamphetamine, antihypertensive agents (Clonidine) and steroids (Fludrocortisone and Hydrocortisone). Study quality was variable, with validity scores ranging from 2 to 19 out of 20. Sample sizes were generally small with half of the 21 studies retrieved having fewer than 50 participants. Very few of the RCTs evaluating pharmacological interventions suggested a beneficial effect.

No benefit was found in CFS patients from treatment with anticholinergic agents, such as Sulbutiamine or Galantamine hydrobromide. One large RCT (n=434) found no significant difference in symptomatic improvement between galantamine and placebo at 16 weeks, whatever the dosage of galantamine hydrobromide (7.5 mg, 15 mg, 22.5 mg, or 30 mg daily). However, adverse events were serious enough to cause patient withdrawal from the study. The evidence suggests that anticholinergic agents provide no meaningful benefit in people with chronic fatigue syndrome.

No benefit was found in patients with CFS from treatment with antidepressants (either in treating symptoms of depression or any of the other outcome measures reported) and adverse effects (e.g. tremor, perspiration) were present. The increased risk of self harm and suicide (particularly in children and teenagers) with the use of antidepressants is underlined by the US Food and Drug Administration (FDA) and other regulatory bodies.[128]

No benefit was found in patients with CFS from treatment with antihypertensive or growth hormone.

Results were mixed in trials of oral NADH (in two low quality RCTs) and melatonin (significant improvements in sleep, vitality and mental health, but worsening of bodily pain in the melatonin group) as well as in the studies of steroid therapy and MAOIs. A trial of dexamphetamine found significant improvements in fatigue in the treated patients but reduced food consumption was a side effect.

Adverse events serious enough to cause people withdrawal from the study were noted with galantamine hydrobromide, phenelzine, fludrocortisone and fluoxetine.

Our literature review found a paper published by Blockmans et al. (2006)[129] A double-blind randomized placebo-controlled crossover study was conducted in 60 CFS patients with concentration difficulties and investigated the effect of methylphenidate, i.e. an amphetamine derivative and stimulatory drug. Clinically significant improvement of the score of the CIS concentration subscale (CIS≤76) was achieved in 13 patients (22%) after treatment with methylphenidate 2x10 mg/day, whereas this occurred in only 3 patients (5%) after placebo (p=0.01). The number needed to treat to achieve clinically significant improvement of concentration disturbances on the CIS was 6 (95% CI, 4.6 to 8.6). In 10 patients (17%) there was a clinically significant response in fatigue scores (≥33% improvement) after treatment with methylphenidate, whereas no patient responded in this way on placebo.

The number needed to treat to achieve a clinically significant response was 6 (95% CI: 3.8 to 14.4). However, no effect was observed on bodily pain, mental health, depression and anxiety. No severe side effect was reported but further studies are needed to investigate the long-term effects of this treatment. Authors recommend this drug for CFS patients with concentration difficulties.

Current evidence shows no overall benefits of pharmacological treatments for CFS (Evidence quality 1A).

Only 1 study (Evidence quality 1A) obtained a beneficial effect of methylphenidate on concentration difficulties and on fatigue (NNT=6); no significant results were obtained for bodily pain, mental health, depression and anxiety; more larger studies are needed with a long-term follow-up to better evaluate both beneficial and side effects of this treatment.

One research protocol was found in the Cochrane Library about pharmacological treatment for CFS adult patients.

1. Rawson KM, Rickards H, Haque S, Ward C. Pharmacological treatments for chronic fatigue syndrome in adults. (Protocol) Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD006813. DOI: 10.1002/14651858.CD006813.

The objective is to assess the efficacy, safety and tolerability of pharmacological treatments for CFS in adults. Pharmacological treatment will be defined as any licensed drug in the British National Formulary (BNF) used to treat the symptoms of CFS. Pharmacological treatments will be broadly classified by drug type into antidepressants, dopamine agonists, analgesics, antiviral agents and Central Nervous System stimulants.

2.5.3.5 Alternative medicine treatments

Trials of complementary therapies included studies on the effectiveness of homeopathy, massage therapy and osteopathy in treating CFS symptoms. One high-quality study of homeopathic treatments on a large sample (n=103) showed a statistically significant improvement in fatigue (p=0.04) and on some physical dimensions of the functional limitations profile (p value is not reported). No adverse effects were reported in either group.

Massage therapy and osteopathy appeared to improve measures of fatigue, back pain and sleep, but the quality of these studies was very poor and the sample size really small (n=20 for massage therapy).

The evidence found on the effects of complementary therapies for CFS is inadequate in terms of quantity and/or quality.

These alternative treatments are considered as an interesting avenue for research and treatment. Two research protocols were found in the Cochrane Library about alternative treatments.

1. Zhang W, Liu ZS, Wu Taixiang, Peng WN. Acupuncture for Chronic Fatigue Syndrome. (Protocol) Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD006010. DOI: 10.1002/14651858.CD006010. The objective is to conduct a systematic review and if possible, a quantitative meta-analysis, with any evidence collected from randomised controlled trials and quasi-randomised trials of acupuncture for adults and children with chronic fatigue syndrome (CFS).
2. Adams D, Wu T, Tai S, Wiebe N, Vohra S. Traditional Chinese medicinal herbs for idiopathic chronic fatigue and chronic fatigue syndrome. (Protocol) Cochrane Database of Systematic Reviews 2007, Issue 1. Art.No.: CD006348. DOI: 10.1002/14651858.CD006348. The objective is to assess the effectiveness of traditional Chinese medicine herbal products in treating idiopathic chronic fatigue and chronic fatigue syndrome.

2.5.3.6 *Supplement treatments*

Eleven studies were reviewed in CRD Report 35 that investigated supplement treatments for CFS patients. Only three of these studies investigating either essentially fatty acids or magnesium were of high quality (1A).

No significant effects were noted in RCTs of general supplements, pollen extract and medicinal mushrooms. A RCT of acclydine and amino acids reported significantly more improvement in IGF-1 levels in the intervention than control group, but no significant difference in global improvement or symptoms ($p < 0.0001$).

Studies that examined essential fatty acid supplements were conflicting, with one high quality RCT (1A; n=50) reporting no improvement and one slightly larger controlled trial (1A; n=63) conducted in patients with post-viral fatigue syndrome (PVFS) reporting an overall beneficial effect. This trial showed greater shifts towards normal levels of cell fatty acid concentration in treatment groups, most of which were statistically significant, as well as improvements in symptom measures.

One small RCT (1A; n=34) showed that magnesium supplements had an overall positive effect of improvement in measures of energy and pain, emotional reactions, general health and laboratory measures, but not in sleep, physical mobility or social isolation. However, two of 34 participants in this study dropped out, 1 because of generalised rash.

One very small RCT (1B) assessed the effects of liver extract in patients with CFS but found no difference in outcomes (activity and energy, mental health, symptoms) between the intervention and control groups.

A RCT of acetyl-L-carnitine and propionyl-L-carnitine (1A) found significant improvements in fatigue and cognitive function associated with treatment. Adverse effects of supplement trials are not well reported as well as reasons for dropping out of the studies (except for magnesium).

Beyond RCTs included in Bagnall' systematic review, McDermott et al.[130] compared a food supplement, the arabinoxylane (BioBran MGN-3) versus placebo for 8 weeks in 71 CFS adult patients. Data were complete in 64/71 patients. Both groups showed marked improvement over the study duration, but without significant differences, except for the social well-being subscale of the WHOQOL-BREF, where improvement was significantly better in the placebo group. There was no significant difference between groups in fatigue severity (change in Chalder physical fatigue subscale from baseline to 8 weeks: -1.5 with BioBran v -1.8 with placebo; difference -0.3, 95% CI -3.2 to + 2.6; $p = 0.84$). No serious adverse effects were reported. Three people on active treatment withdrew because of minor side-effects (mild nausea, exacerbation of fatigue, and irritable bowel symptoms, respectively) and one person withdrew from the placebo group because of worsening fatigue (p value not provided).

Another recent RCT assessed the effect of Acclydine on fatigue severity, functional impairment, and biologically active IGF1 level (IGFBP3/IGF1 ratio) in CFS adult patients.[131] No differences were found in IGF1 status in CFS patients compared to healthy matched neighbourhood controls. In addition, the results of this clinical trial do not demonstrate any benefit of Acclydine over placebo in the treatment of CFS. The negative results of this trial are important: Acclydine is expensive and is available without prescription on the Internet, making it available to patients potentially without a doctor's oversight.

Evidence is insufficient to support a beneficial effect of dietary supplements, including essential fatty acids in CFS (Evidence quality 1A).

2.5.3.7 *Other treatments*

One controlled trial of combination treatment (including medical treatment of symptoms plus anxiety/affective disorder and CBT) in patients with CFS was also included in the CRD Report 35.[1] This controlled trial included 71 patients, but only 22 of the 71 original participants were followed up (17 in the intervention group and 5 in the control group).

In the intervention group, 15 returned to work (88%), while only 2 were professionally active in the control group (40%). However, this study scored very poorly on the validity assessment (2C).

A controlled trial of 'broad-based management' (mainly information and advices concerning energy and exercise, food and diet) in adults and children diagnosed with post-infectious fatigue syndrome found significant improvements in the intervention group in measurements of fatigue, somatic symptoms and self-efficacy. However, this study had a low quality level (2C) indicating that these results should be treated with caution.

A very small controlled trial (n=12) of a buddy/mentor programme (emotional support, social companionship and instrumental support) found significant improvements in the treatment group compared to control for self-reported fatigue severity but not for any of the other six outcomes investigated (positive thinking, depression, psychological distress, perceived stress, coping strategies and perceived social support).

A trial of 'group therapy' (unstructured discussions, not well described) found no significant effects of treatment.

An unpublished trial of a low sugar, low yeast diet, compared to healthy eating, also found no significant effect of treatment.

One high quality level RCT (1A) of multiple symptom-based treatments (including supplements) found significant improvements in favour of the treatment group in symptoms scores, overall response and fibromyalgia-specific symptoms. However, it is important to note that all patients included in this RCT meet criteria for fibromyalgia.

2.5.4 Recommendations for treatment

According to all these results, following recommendations for treatment can be formulated, in agreement with the guidelines proposed by NICE[10,2]:

2.5.4.1 General management strategies after diagnosis

- After diagnosis, manage symptoms as in usual clinical practice, which may include drugs and dietary changes. Specific drug treatment for children and young people should be started by a paediatrician. Other interventions that may improve function and quality of life include sleep management (for example, identifying common changes in sleep patterns seen in CFS such as insomnia, hypersomnia, sleep reversal, altered sleep–wake cycle and non-refreshing sleep), appropriate use of rest periods, relaxation, and further dietary changes, as needed. Some sleep problems need a specific intervention. For example, altered circadian rhythms (sleep-wake cycles) may require manipulation of sunlight exposure.
- Do not encourage daytime sleeping and naps which may disrupt the sleep–wake cycle without improving physical or mental functioning. Patients would limit the rest periods to 30 minutes at a time and introduce 'low level' physical and cognitive activities (depending on the severity of symptoms).
- During a setback (or relapse) with increased symptoms, advise patients to maintain physical activity if possible. If not possible, aim for a gradual return to previous exercise and functional routines.
- Advise patients to maintain a well balanced diet with regular eating. Dietary supplements (including vitamins and minerals) and complementary therapies are not recommended as there is insufficient evidence of benefit. Exclusion diets are not generally recommended for CFS, but many people find them helpful in managing symptoms, including bowel symptoms.
- Advise on fitness for work and education and recommend flexible adjustments or adaptations to work or studies for return to these when the patient is ready and fit enough. With the patient's consent,

liaise with employers, education providers, and support services such as occupational health services and schools.

- Consider referral to a specialist on the basis of the person's needs and symptoms: offer referral within six months of presentation to those with mild symptoms, within three to four months to those with moderate symptoms, and immediately to those with severe symptoms.
- Do not offer CFS patients advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply 'go to the gym' or 'exercise more') that may worsen symptoms; specialist management programmes delivered by practitioners with no experience in the condition.

2.5.4.2 Pharmacological treatments

Treatments such as antidepressants, glucocorticoids, mineralocorticoids, dexamphetamine, methylphenidate, thyroxine, antibiotics and antiviral agents are not recommended as evidence for their overall benefit is equivocal.

Adverse events serious enough to cause people withdrawal from the study were noted with galantamine hydrobromide, phenelzine, fludrocortisone, fluoxetine, vaccination with staphylococcus toxoid, immunomodulators and antiviral agents. Because macrolide use is evidently associated with the emergence of macrolide-resistant *Streptococcus pneumoniae* and *S. pyogenes*, unnecessary prescribing of macrolides should be avoided.

Risks with use of these all products are greater than benefits potentially obtained.

2.5.4.3 Specialist care

- Collaborate with the patient on an individualised programme, aiming to sustain or gradually extend the patient's physical, emotional, and cognitive capacity, and to manage the physical and emotional impact of symptoms on the individual and his or her carers.
- Offer cognitive behaviour therapy **or** graded exercise therapy to people with mild or moderate CFS and provide these therapies to those who choose them, as these interventions show clearest evidence of benefit. These interventions should only be delivered by appropriately trained professionals with experience in CFS, and with appropriate clinical supervision.
- Diagnosis, investigation, management, and monitoring for people with severe CFS should be supervised or supported by a specialist in the condition. This may include providing domiciliary services or using methods such as telephone or email as appropriate.

In agreement with NICE guidelines, it can be recommended:

- **In primary care, early management of symptoms, advice on activities and occupation, and criteria for specialist referral are emphasised. Making an accurate diagnosis and considering differential diagnoses and co-existing morbidity.**
- **Referral should be immediately offered if: the patient is a child within 6 weeks of presentation; the patient has severe CFS symptoms.**
- **Referral should also be considered after 6 months in mild CFS, or 3-4 months in moderate CFS, depending on symptoms and comorbidity.**
- **In specialist care, CBT and pacing/GET should be available, because these treatments show the clearest research evidence of benefit.**
- **No study investigated the added value of the combination of CBT and GET. Combining these therapies should take into account incremental costs compared to incremental effectiveness**
- **Pharmacological treatments (such as antidepressants, glucocorticoids, mineralocorticoids, dexamphetamine, methylphenidate, thyroxine, antibiotics and antiviral agents) are not recommended as evidence for their overall benefit is equivocal.**

More generally,

- **Guidelines emphasise the need to negotiate management programmes with the patient and not to coerce them into specific treatments.**
- **Pacing is the least complicated strategy available to patients who wish to manage their energy levels.**
- **Patients who are reluctant to CBT (psychological treatment) to treat a 'physical condition' will prefer self-management techniques and GET that encourage a behavioural while acknowledging the physical aspects of the illness.**
- **GET is not appropriate for patients with brain abnormalities or evidence of immune activation; this treatment is more beneficial for people who are avoiding activity due to fear or misinformation, if their symptoms are not closely linked to exertion, or if they are well on the way to recovery.**
- **The exercise program should be tailored to each CFS patient. For deconditioned CFS patients, low level strengthening exercises prior to initiating an aerobic program is recommended.**
- **CBT and GET require trained specialists having an experience with CFS; pacing does not require a specialist, but can be adequately explained by a GP or a practice nurse.**

2.5.5 Pacing, cognitive behavioural therapy or graded exercise therapy: current research and therapy manuals developed by experts

Cognitive behaviour therapy (CBT) and GET were found in all systematic reviews as the most promising treatments for CFS. No other treatments for CFS have so far been shown to be helpful in more than one RCT. Both these approaches encourage gradual increases in activity according to a pre-determined plan, to reduce the physiological effects of deconditioning which are considered by some to play a major role in the perpetuation and exacerbation of fatigue.[79]

However, the goals, modalities and indications of these treatment strategies as well as their implementation in routine clinical practice remain a matter of controversy.[132] While some authors have put forward that cognitive behavioural therapy in CFS should aim at complete recovery[133], others have taken the view that searching for 'a new equilibrium' in life – often at a lower level of functioning – may optimize patients' chances of restoring effort tolerance.

Moreover, surveys conducted by patients groups, as well as studies assessing the effect of graded exercise, have indicated that many patients cannot increase activity levels beyond a certain point, that the outcomes tend to be modest, drop-out rates were fairly high, and post-trial effects were not reflected in an objective increase of daily activity levels.[134,80]

Pacing can be considered as an additional therapeutic option available to health professionals, and that for optimal results, it should be offered as part of a multi-disciplinary, multi-dimensional programme where interventions can be combined to meet individual needs and changing circumstances.[135,136]

GET assumes that there is no underlying disease process causing the fatigue; consequently, this treatment strategy is not an appropriate first line treatment for patients with brain abnormalities or evidence of immune activation.[132] However, if people are avoiding activity due to fear or misinformation, if their symptoms are not closely linked to exertion, or if they are well on the way to recovery, then a rehabilitation programme which includes GET is likely to be more beneficial than pacing and similar strategies.[132]

While evidence exists in favour of CBT and GET, there is still insufficient evidence to recommend adaptative pacing therapy (APT). In a similar way there is little RCT evidence of the efficacy of specialist medical care. There is therefore an urgent need to: (a) compare the supplementary therapies of both CBT and GET with both APT and standardised specialist medical care (SSMC) alone, seeking evidence of both benefit and harm (b) compare supplementary APT against SSMC alone and (c) compare the

supplementary therapies of APT, CBT and GET in order to clarify differential predictors and mechanisms of change.

These objectives are currently pursued by the PACE trial (see http://www.pacetrial.org/ accessed on May, 20th 2008). This large-scale trial is the first in the world to test and compare the effectiveness of four of the main treatments currently available for people suffering from chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME). These are adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and standardised specialist medical care. All of the treatments offer ways for patients to deal with and improve the symptoms of CFS and its effects on disability. The participants in the trial are randomly allocated to one of the treatments and then given a 12-month programme involving appointments with specialised doctors and, for three of the four treatment groups, therapists. Participants' progress is closely monitored by specially-trained research nurses or assistants. The five-year trial will involve 600 participants, aged 18 and over, in Scotland and England. All have to be referred from the specialist hospital CFS clinics involved in the trial and these are based in Edinburgh, Oxford and three London hospitals. The whole protocol can be found at: http://www.biomedcentral.com/1471-2377/7/6. The PACE trial opened to recruitment in March 2005.

PACING[136]

Pacing makes no assumptions about aetiology but adopts a precautionary principle, i.e. pacing helps patients to remain as active as possible while avoiding over-exertion. This strategy is applied to daily activities. An important difference with GET (or CBT) is that in pacing it is the patient who decides whether or not to continue an activity. Although a gradual increase in activity levels is permitted, the rule is that they should stop when the initial mild fatigue turns into a more unpleasant sensation, or where arms or legs begin to feel weak. The patient may choose to respond either by resting, or if the fatigue is localised, by switching to an activity which uses a different muscle group. The same rule is adopted for mental activities such as reading, speaking on the telephone and using the computer. In practice, pacing means that patients should plan their day to include plenty of time for rest and relaxation. There is no need to divide up minor tasks, but it is often helpful to restrict the number of demanding or stressful activities to one a day. The remainder of that day can then be spent doing less exhausting tasks, or resting, depending on how the patient feels. After a few weeks, most individuals will know from experience how they tend to respond to various activities and what they can manage per day without exacerbating their condition.

Once patients are able to evaluate what they can tolerate, they can make provisional plans for the days or weeks ahead, as long as they respond to any symptoms as they occur. This version of pacing is the least complicated strategy available to patients who wish to manage their energy levels. However, some patients have difficulties with the self-discipline required, and simply prefer a more structured programme, such as CBT and GET.

Combining pacing and switching, i.e. changing activities to avoid tiring specific muscle groups, is recommended. For instance, if a person has been walking, the advice is to stop before, or at the first signs of fatigue and to switch to something involving different muscles, e.g. reading, watching TV, washing or ironing. Using this approach, it may be possible to further reduce the duration and severity of post-exertional fatigue and hence extend the energy available for everyday tasks.

Pacing requires no specialist training. A GP or practice nurse can explain the basic rules, and if required, assist patients who have problems in identifying their baseline. For the more severely affected, pacing can be included in a multi-dimensional programme or other intervention which also provides medical care, emotional support, counselling, and dietary advice.[97,135]

COGNITIVE BEHAVIOURAL THERAPY (CBT)

Cognitive behavioural therapy is a more complex therapy than GET, requiring highly trained therapists, and is therefore less readily available.

Cognitive behaviour therapy should follow the usual principles and include asking the patient to self monitor activity, rest, thoughts, feelings, and behaviours; discussing with the patient his or her adjustment to the diagnosis; and encouraging acceptance of current functional limitations.

A course of CBT should be delivered:

- by a healthcare professional with appropriate training in CBT and experience in CFS, under clinical supervision, and with close adherence to protocols;
- one-to-one if possible.

Plan CBT for a person with CFS according to the usual principles of CBT, and include:

- Acknowledging and validating the person's symptoms and condition.
- Explaining the CBT approach in CFS, such as the relationship between thoughts, feelings, behaviours and symptoms, and the distinction between causal and perpetuating factors.
- Discussing the person's attitudes and expectations.
- Developing a supportive and collaborative therapeutic relationship.
- Developing a shared formulation and understanding of factors that affect CFS symptoms.
- Agreeing therapeutic goals.
- Tailoring treatment to the person's needs and level of functioning.
- Recording and analysing patterns of activity and rest, and thoughts, feelings and behaviours (self-monitoring).
- Establishing a stable and maintainable activity level (baseline) followed by a gradual and mutually agreed increase in activity.
- Challenging thoughts and expectations that may affect symptom improvement and outcomes.
- Addressing complex adjustment to diagnosis and acceptance of current functional limitations.
- Developing awareness of thoughts, expectations or beliefs and defining fatigue-related cognitions and behaviour.
- Identifying perpetuating factors that may maintain or exacerbate CFS symptoms to increase the person's self-efficacy (sense of control over symptoms).
- Addressing any over-vigilance to symptoms and related checking or reassurance-seeking behaviours by providing physiological explanations of symptoms and using refocusing/distraction techniques.
- Problem solving using activity management and homework tasks to test out alternative thoughts or beliefs, such as undertaking pleasure and mastery tasks (tasks that are enjoyable and give a sense of accomplishment).
- Building on existing assertion and communication skills to set appropriate limits on activity.
- Managing sleep problems, for example by addressing any unhelpful beliefs about sleep, behavioural approaches to sleep disturbance, stress management, and/or relaxation training.

However, some patients with CFS are reluctant to undertake psychological treatments, such as cognitive behavioural therapy, for what they believe to be a physical condition. In this case, specialists will preferably propose pacing self-management techniques that encourage a behavioural change and at the same time acknowledge the physical aspects of the illness.[137]

GRADED EXERCISE THERAPY (GET)

Graded exercise therapy should be delivered by a suitably trained GET therapist with experience in CFS, under appropriate clinical supervision and preferably one-to-one. GET should include the establishment of a baseline followed by planned increases in duration of low intensity physical activity, followed by gradual increases in intensity leading to aerobic exercise (which increases the pulse rate). It should be based on current level of activities and daily routines and on the patient's own goals. Both patient and healthcare professional should recognise that it may take weeks to years to achieve these goals.

Although graded exercise therapy is recommended for CFS patients, exercise can exacerbate symptoms in chronic fatigue syndrome and provoke post-exertional malaise if too-vigorous exercise/activity is prescribed. Designing and implementing an exercise programme for chronic fatigue syndrome have to take into account this adverse effect in order to deliver a programme with no detrimental effects on the pathophysiology of the condition, in particular to guarantee treatment compliance.[137]

Guidelines to implement such a graded exercise therapy programme are proposed both by Wallman et al (2005)[138] and by Nijs et al. (2008).[137]

EXAMPLE OF STRUCTURED PROTOCOL FOR EXERCISE SESSIONS

Wallman et al. (2005)[138] have described the graded exercise program used in their randomised controlled trial.[82] According to the authors, this program has been successfully implemented in a clinical practice. It includes the concept of pacing and is aimed at non-bed-bound, sedentary patients with CFS, as well as those already undertaking minimal aerobic exercise (i.e., no more than three sessions per week of 20 minutes' duration). The protocol described here was never associated with any major relapse, helped to prevent CFS patients overdoing physical activity and can halt further deconditioning. The exercise sessions are *in addition* to normal activities, and some initial aches and pains are usual when beginning exercise for the first time.

Patients have:

- to follow their heart rate during exercise sessions (checked with a heart rate monitor or by assessing pulse rate)
- to rate their perceived exertion (RPE - Borg scale in Table 4) on completion of each exercise session in order to average values each fortnight. The averaged RPE value forms the basis for determining the duration of future exercise sessions
- to monitor progress over time and link poor performance with a possible emotional or physiological event (exercise diary).

Table 4. Borg's rating of Perceived Exertion Scale

Perceived exertion	Rating
	6
Very, very light	7
	8
Very light	9
	10
Fairly light	11
	12
Somewhat hard	13
	14
Hard	15
	16
Very hard	17
	18
Very, very hard	19
	20

Source. Borg (1982)[139]

The exercise program, based on a 'pacing' strategy[140]:

- Once every second day
- Exercises that use the major muscles of the body (walking, jogging, swimming or cycling)
- Duration of each exercise session during the first fortnight should be negotiated with the patient - from 1 to 10 minutes, depending on individual physical capabilities (except for patient already exercising, the duration should be one that the individual is currently coping with consistently).
- Intensity of the exercise: a pace that the individual can perform comfortably, determined on a typical day for symptom severity (not better or worse than usual). The average peak heart rate when exercising at a comfortable pace on a typical day should be recorded, with this intensity representing the patient's target heart rate (± 3 bpm) for future sessions. The "warm-up" time that it takes for heart rate to reach this target is included in the overall exercise duration.
- If the initial session was perceived by the patient too easy (i.e. an overall RPE score ≤ 9), a slight increase in duration could be considered. If the RPE score was > 14, then propose a decrease in duration of subsequent sessions to a time period that elicits an RPE score of 11–14.
- At the end of each fortnight, patients should contact their doctor to determine the next fortnight's exercise prescription. If patients coped with the exercise regimen, did not experience a major relapse, and reported averaged fortnightly RPE values of 14 or less, then the exercise duration for the following fortnight should be increased by 2–5 minutes. If the average RPE score was 15 or higher, then the exercise duration should be reduced to a time period that elicits an averaged fortnightly RPE score of 11–14.
- Same procedure and recommendations for the next and subsequent fortnights, in that individual target heart rate is kept constant, and RPE scores are recorded after each exercise session and averaged at the end of each fortnight.
- Some days, patients feel comparatively well; however, to avoid relapses, they *must* adhere to their current exercise regimen and must *not* perform any extra exercise above this level. Same rule for normal everyday physical tasks, such as housework and gardening.
- On days when symptoms are worse, patients should either shorten the session to a time they consider manageable or, if feeling particularly unwell, abandon the session altogether, and commence the exercise program again when symptoms subside to a tolerable level.
- When recommencing exercise, the pace should be comfortable, while the duration should be reduced to a time that the individual feels is manageable and elicits an RPE score of 11–14. Patients should then continue at this modified duration for a fortnight and increase this time period for the subsequent fortnight only if the averaged fortnightly RPE score was 14 or lower.
- Finally, if the duration of exercise reaches 30 minutes, patients could consider increasing the intensity of sections of the exercise session. An example of this would be where the first minute of every 10 minute section of the session is performed at a higher intensity (RPE, 15–16). The number of higher intensity minutes can be marginally increased each fortnight if averaged fortnightly.
- RPE scores fall within the guidelines described earlier.

FROM A STABILIZATION PHASE TO A GRADING PHASE

In their paper, Nijs et al. (2008)[137] recommend the same exercise scheme as Wallman et al. (2005)[138]. However, they summarized the process in a simpler algorithm. As Wallman, they recommend to CFS patients learning to estimate their current physical capabilities prior to commencing an activity, keeping in mind the regular fluctuating nature of their symptoms. Firstly, a stabilization phase is proposed according to the following scheme:

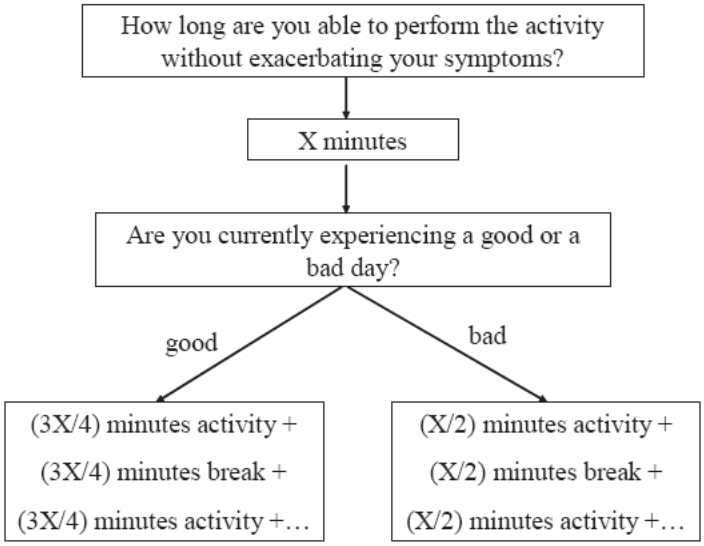


Fig. 1. Scheme for teaching a patient with chronic fatigue syndrome the pacing self-management principles (stabilization phase). X: number of minutes a patient feels to be able to perform the activity without exacerbating their symptoms. Example: a CFS patient believes she is capable of walking for 20 min without exacerbating her symptoms and is currently having a relatively good day. We advise her to walk for no longer than 15 min followed by a 15-min break. At that point the patient is instructed to reassess her health status: if her symptoms are still approximate to prior to commencing the walking exercise, then she is allowed to start a second 15-min bout of walking. On a bad day she is instructed to further decrease the walking duration to 10 min (i.e. 50% of 20 min).

Source: Nijs et al. (2008)[137]

When patients are able to manage their daily activity (i.e. symptom fluctuation is reduced to a manageable level) (stabilization phase), the therapist can then start to progress activity and exercise levels (grading phase). Patients who are functioning within the limits of their individual physical capabilities do not require pacing self-management (stabilization phase) and can immediately enter the grading phase, according to the following scheme:

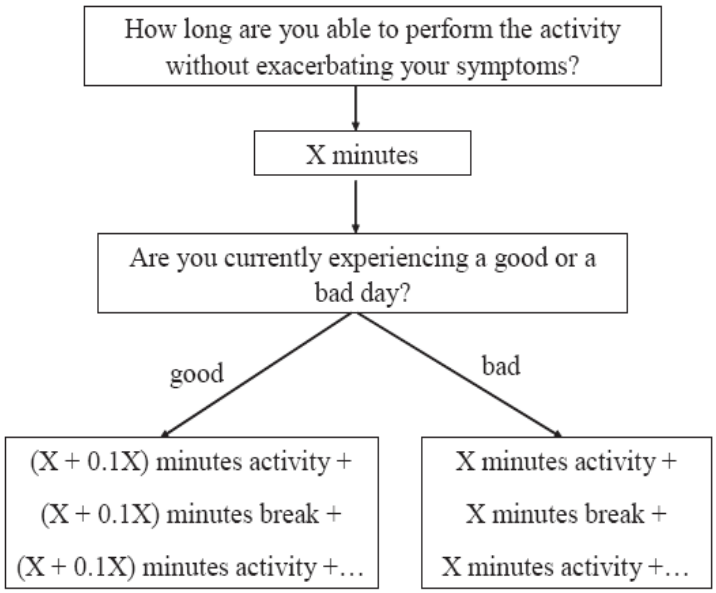


Fig. 2. Scheme for teaching a patient with chronic fatigue syndrome the pacing self-management principles (grading phase). X: number of minutes a patient feels to be able to perform the activity without exacerbating their symptoms.
Source: Nijs et al. (2008)[137]

2.5.6 Occupational management

A systematic review conducted by NHS-Plus Evidence based guidelines (2006)[16] did not identify any primary research on the best way to manage return to work in individuals with CFS.

However, Rimes and Chalder (2005) give some advices for employers (level of evidence 2C).[78]

According to these authors, the following points can be considered for employees with CFS who are currently off work but who have recovered sufficiently for a return to work:

- There would be liaison between the employee, occupational health, management and human resources.
- The occupational health professional would liaise, with the employee's consent, with his/her general practitioner, consultant or treating practitioner.
- Employer and employee would explore whether the employee perceives that any work issues have contributed to or are contributing to fatigue. This would include a full exploration of all aspects of the case, including work satisfaction and interpersonal issues.
- An individualised return to work plan would be developed. This may include:[78]
  - building up work or work-related skills at home or in a voluntary position initially
  - gradually increasing hours of work (the employee may need to start with a dramatically reduced workload and hours of work, gradually increasing both, depending on progress)
  - regular breaks
  - regular review by an occupational health professional.

3 ECONOMIC EVALUATION OF CFS EVIDENCE-BASED TREATMENTS: A LITERATURE REVIEW

3.1 INTRODUCTION AND LITERATURE SEARCH

The aim of this chapter was to perform a detailed and critical appraisal of the published economic evaluations of evidence-based treatments against chronic fatigue syndrome (CFS).

As stated in previous chapters, cognitive behavioural therapy (CBT) and graded exercise therapy (GET) can be considered as efficacious treatments against CFS. However, economic evaluations of those interventions are rare, although information about the relative cost-effectiveness of such treatments (and potentially other treatments) is desirable.

The previous search of the relevant literature on the treatments' effectiveness (see chapter 2) already allowed the identification of two articles about the cost-effectiveness of therapies against CFS.[141, 142] This search also allowed the identification of UK guidelines about the management of CFS in which a limited overview of the health economic evidence about CFS treatment is reported.[2]

In order to capture all the available economic evidence on CFS treatment, additional searches were performed by consulting various databases up to the end of March 2008. The HTA (CRD) database was questioned to retrieve published health technology assessment (HTA) reports on the topic. The EED (CRD), Medline (OVID), EMBASE and the Cochrane Library of Systematic Reviews databases were questioned to retrieve additional full economic evaluations (i.e. the studies comparing at least two alternative treatments in terms of costs and outcomes, see classification in appendix 1) and potential reviews of full economic evaluations of CBT or GET. No language or period restrictions were applied. Details of the searches can be found in the appendix 2.

Altogether, the searches of the various databases returned 8 unique citations which were assessed on the basis of their title and abstract first, next on the basis of their full-text. Following this process, only one additional study pertaining to the economic evaluation of CBT versus counselling therapy (CT) was identified.[143] Two letters to editor[144, 145] commenting the economic evaluation of Severens et al.[142] were only retained as background information.

The full text articles of the three economic evaluations and of the two letters were retrieved.[141,142,143,144, 145] The three economic evaluations were then critically appraised and summarized in in-house data extraction forms (see appendix 3).

In the following paragraphs we present the main characteristics of the three economic evaluations together with their results. Since they specifically pertain to CFS patients, which are the focus of this report, the characteristics and the findings of the economic evaluation of Severens et al.[142] are first presented. The findings of Chisholm et al.[143] and McCrone et al.[141] are subsequently presented. These should rather be considered as informative since the target population of those studies is chronic fatigue patients, of which only a subset are CFS patients.

During an update (end of May 2008) of the literature search about the economic evaluations of CFS treatments, the recent study of Annemans et al.[146] was identified. This study was however not further considered for inclusion in the current review since it targets patients with fibromyalgia syndrome and since it is not a full economic evaluation.

3.2 MAIN CHARACTERISTICS OF THE ECONOMIC EVALUATIONS

An overview of the general characteristics of the three economic evaluations is presented in Table 5. All three studies were published before the year 2004 and were performed in Europe. Further all were RCT-based piggy-backed economic evaluations.

Table 5. General characteristics of the economic evaluations

Author	Publication year	Country	Analysis		Time horizon	Discount rate	Costing perspective: cost items included
			CUA	CEA			
Severens et al.	2004	Netherlands	X	X	14 months	na	Direct medical costs Direct non-medical costs Indirect costs
McCrone et al.	2004	UK	-	X	8 months	na	Direct medical costs Direct non-medical costs
Chisholm et al.	2001	UK	-	X	6 months	na	Direct medical costs Direct non-medical costs Indirect costs

CUA: cost-utility analysis; CEA: cost-effectiveness analysis; na: not applicable

3.2.1 Analytical technique and outcome measures

Severens et al.[142] report their results in terms of cost-effectiveness ratios (Table 5). As CFS treatments are not expected to impact much on survival, the number of life-years gained (LYG) was not used as a measure of outcome, but rather surrogate measures of the improvements of the main CFS symptoms, i.e. number of patients with a clinically significant improvement in fatigue score. The change in fatigue was measured by the Checklist Individual Strength (CIS) Questionnaire.[69] Further, Severens et al.[142] also report their results in terms of cost-utility ratios, with outcomes expressed as quality-adjusted life-years (Table 5). The EQ-5D questionnaire[147] was used to collect patients' preferences on their health state but the valuation set used to derive utilities is not explicitly stated by the authors.

McCrone et al.[141] and Chisholm et al.[143] only report their results in terms of cost-effectiveness ratios. The measures of outcome in those studies were the mean improvement in fatigue score[141, 143] and the number of patients with a clinically significant improvement in fatigue score.[141] In both studies, the change in fatigue was assessed by the Chalder Fatigue Questionnaire.[68]

3.2.2 Perspective

The costs categories considered by Severens et al.[142] are direct medical costs (i.e. the costs of the intervention and other direct medical costs such as outpatient visits, medications…), direct non-medical costs (i.e. the costs of travelling to seek care, informal home care support[e], visits to practitioners for alternative medicine…) and indirect (or productivity) costs (i.e. the cost related to the absence of the patient from work due to the condition) (Table 5). In this study,[142] those three cost categories were combined to present the results under a "Societal" perspective. The results were also presented under a "Payers" perspective by ignoring the indirect costs category and by combining only the direct medical cost with the direct non-medical cost categories.

The cost categories considered in McCrone et al.[141] and in Chisholm et al.[143] consisted also in direct medical and direct non-medical costs. Indirect (productivity) costs were further considered in Chisholm et al.[143] only.

The combination of these cost categories for the computation of the cost-effectiveness was however different between both studies, so that their results cannot be compared on the basis of a unique costing perspective. In Chisholm et al.,[143] results are presented including direct medical costs alone ("Health Care Payers" perspective) and in combination with direct non-medical costs and indirect costs ("Societal" perspective).

In McCrone et al.,[141] results are only presented by combining direct medical costs with direct non-medical costs ("Payers" perspective).

3.2.3 Time horizon and discount rate

The time horizon of the economic evaluations was limited by the duration of the follow-up period of the trials they rest on. This follow-up period was 14 months in Severens et

[e] Informal home care is defined as the time spent by friends or relatives for personal support, child care, help in or around the house, help outside the home or other tasks.

al.[142] based on the Prins et al.[88] trial (Table 5). The time horizon in Severens et al.[142] is certainly long enough to capture important clinical changes such as improvements in fatigue. However, due to the chronic nature of CFS and since CFS may require maintenance treatment later in time, costs and outcomes should be tracked for a longer timeframe, ideally over a patient's lifetime. Severens et al.[142] did not use modelling to extrapolate their results to longer timeframes.

The follow-up period was limited to 6 months in Chisholm et al.[143] (based on the Ridsdale et al.[148] trial) and to 8 months in McCrone et al.[141] (based on an other Ridsdale et al.[149] trial).

Given their short timeframe, none of the studies applied discounting (Table 5).

3.2.4 Population

In Severens et al.[142] and its underlying trial,[88] the target population consisted in patients with CFS. Patients were included if they were aged 18 to 60 years, if they had a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength (criteria for CFS according to Fukuda et al.[12]) and if they had a score of 800 or more on the Sickness Impact Profile.

In Chisholm et al.[143] and in McCrone et al.,[141] the target population was more broadly defined and included patients with chronic fatigue. Only a subset of those patients was thus classified as having CFS (about 30% of the trial population in McCrone et al.[141]) In those studies and in their underlying trials,[148,149] patients were included if they were aged 16 to 75 years, if they had complaints of fatigue as a main or important problem and if their fatigue symptoms lasted for more than 3 months. In those studies, sub-group analyses pertaining only to the subset of CFS patients were not performed.

3.2.5 Intervention / comparators

As explained in a previous chapter (section 2.5.3.1.), cognitive behaviour therapy (CBT) is a combination of cognitive and behaviour therapy. CBT is delivered by trained therapists and includes energy/activity management, the establishment of a sleep routine, goal setting and psychological support.

In Severens et al.,[142] the alternative therapeutic strategies compared to CBT were guided support group (SG) and a do nothing (DN) strategy (Table 6). SG consisted in meetings between groups of CFS patients and open discussions about their own condition, under the supervision of a single therapist. The DN strategy represented the medical seeking behaviour of CFS patients as in current practice.

In McCrone et al.[141] and in Chisholm et al.,[143] the therapeutic strategies compared to CBT were graded exercise therapy (GET)[141] and counselling therapy (CT)[143] (Table 6). GET consisted in structured and progressively increasing activities or exercises under the supervision of a therapist, with the aim to improve the patient's physical condition. CT consisted in discussions among CFS patients and a trained counsellor, allowing the patient to share his concerns and difficulties in a supportive environment.

Table 6. Comparators to CBT

Author	Publication year	Cognitive Behaviour Therapy compared with		Therapy intensity	
		Intervention	Trial source	CBT	Comparator
Severens et al.	2004	Guided Support Group (SG) Do Nothing (DN)	Prins et al., 2001	16 x 60 min	SG: 11 x 90 min
McCrone et al.	2004	Graded Exercise Therapy (GET)	Ridsdale et al., 2004	6 x 45 min	GET: 6 x 45 min
Chisholm et al.	2001	Counselling Therapy (CT)	Ridsdale et al., 2001	6 x 50 min	CT: 6 x 50 min

CBT: cognitive behaviour therapy; SG: guided support group; GET: graded exercise therapy; CT: counselling therapy

In Severens et al.,[142] the various therapeutic strategies administered to CFS patients consisted in 16 sessions of 60 minutes each for CBT and 11 sessions of 90 minutes each for SG (Table 6).

The treatment pattern for chronic fatigue patients was less intensive than for CFS patients since only 6 sessions (of CBT, GET or CT) of 45-50 minutes each were administered to chronic fatigue patients in McCrone et al.[141] and in Chisholm et al.[143]

3.2.6 Unit costs of the therapeutic strategies

The original unit costs of the therapeutic strategies are reported in Table 8. To improve the comparison between studies, original costs were standardized in common euros of the year 2007 using Consumer Price Indices and Purchasing Power Parities (Table 7).

Table 7. Correction for price inflation and currency conversion

Author	Publication year	Country	Costing year	Original currency	CPI multiplicator[a]	PPP multiplicator
Severens et al.	2004	Netherlands	1998	€	1,21653	1,00679
McCrone et al.	2004	UK	2001	£	1,11166	1,35671
Chisholm et al.	2001	UK	1998	£	1,14913	1,35671

a. From costing year to 2007; Consumer Price Indices (CPI) and Purchasing Power Parities (PPP) were obtained from the OECD website, accessed on April the 24th 2008 (www.stats.oecd.org)

The cost of a CBT session greatly differed according to the population targeted in the studies. In Severens et al.,[142] a 60-minutes CBT session delivered to CFS patients costs €114 (Table 8), while in McCrone et al.[141] and in Chisholm et al.,[143] a 45-50-minutes CBT session delivered to chronic fatigue patients is worth about the half (€50).

In the three economic evaluations, the unit costs for CBT cover the actual time spent by the therapist (for patients-based or administrative activities) and his training. Beside this, the unit costs for CBT in Severens et al.[142] also cover an extensive diagnostic procedure to identify CFS patients eligible to this form of therapy. Without those diagnostic costs, the unit costs of CBT for CFS patients (€83 per session) still remain higher than those for chronic fatigue patients.[f]

Table 8. Cost per CBT, SG, GET and CT session

Author	Publication year	Country	CBT Intensity	Original cost per session				Cost in 2007 Belgian €			
				CBT	SG	GET	CT	CBT	SG	GET	CT
Severens et al.[a]	2004	Netherlands	16 x 60 min	€93,1	€38,5	-	-	€114,1	€47,2	-	-
McCrone et al.	2004	UK	6 x 45 min	£30,0	-	£30,8	-	€45,2	-	€46,4	-
Chisholm et al.	2001	UK	6 x 50 min	£33,3	-	-	£23,3	€52,0	-	-	€36,4

a. In Severens et al., the additional cost of extensive diagnostic activities is shared out in the cost of a CBT session. Without those diagnostic costs, the cost of a CBT session becomes €82,6 (cost in 2007 €); CBT: cognitive behaviour therapy; SG: guided support group; GET graded exercise therapy; CT: counselling therapy

The unit costs for other therapies appeared to be relatively similar (Table 8). With the exception of McCrone et al.,[141] a CBT session is estimated to be more expensive than its comparators.

3.3 RESULTS OF THE ECONOMIC EVALUATIONS

3.3.1 Incremental costs

A breakdown of the mean costs per patient for each therapy considered is presented in Table 9, together with the incremental costs of CBT over its comparators.

f The higher unit cost of a CBT session in The Netherlands, even after deduction of the diagnostic costs, may be due to the fact that CBT was administered in the outpatient department of a university hospital in this country, whereas it was administered in community care in The UK.

Table 9. Mean and incremental costs (95% confidence interval)

Author (Publication year) Time horizon	Cost categories	Mean total costs					Incremental costs: CBT versus		
		CBT	SG[a]	DN	GET	CT	DN	GET	CT
Original costs									
Severens et al.	Intervention costs	€1490	€424	€0	-	-	€1490[b]	-	-
(2004)	Other direct medical costs	€556	€1184	€790	-	-	-€234[b]	-	-
14 months	Direct non-medical costs	€488	€989	€714	-	-	-€226[b]	-	-
	Indirect costs	€20490	€15165	€22353	-	-	-€1863[b]	-	-
	Total costs - Payers	*€2534*	*€2597*	*€1504*	-	-	*€1030*[b]	-	-
	Total costs - Society	*€23024*	*€17762*	*€23857*	-	-	*-€833*[b]	-	-
McCrone et al.	Direct medical costs	Not stated	-	-	Not stated	-	-	Not stated	-
(2004)	Direct non-medical costs	Not stated	-	-	Not stated	-	-	Not stated	-
8 months	*Total costs - Payers*	*Not stated*	-	-	*Not stated*	-	-	*-£193 (-£946–458)*[c]	-
Chisholm et al.	Intervention costs	£164 (150–181)	-	-	-	£109 (96–119)	-	-	£55 (35–76)
(2001)	Other direct medical costs	-£36 (-145–81)	-	-	-	-£43 (-114–36)	-	-	£4 (-124–144)
6 months	Direct non-medical + indirect costs	-£125 (-1048–645)	-	-	-	-£241 (-860–43)	-	-	£116 (-976–1086)
	Total costs - HCP	*£129 (23–242)*	-	-	-	*£65 (-6–146)*	-	-	*£63 (-42–258)*
	Total costs - Society	*£4 (-928–822)*	-	-	-	*-£176 (-793–410)*	-	-	*£180 (-968–1103)*
Costs in 2007 Belgian €									
Severens et al.	Intervention costs	€1825	€519	€0	-	-	€1825[b]	-	-
(2004)	Other direct medical costs	€681	€1450	€968	-	-	-€287[b]	-	-
14 months	Direct non-medical costs	€598	€1211	€874	-	-	-€277[b]	-	-
	Indirect costs	€25096	€18574	€27378	-	-	-€1863[b]	-	-
	Total costs - Payers	*€3104*	*€3181*	*€1842*	-	-	*€1262*[b]	-	-
	Total costs - Society	*€28199*	*€21755*	*€29220*	-	-	*-€1020*[b]	-	-
McCrone et al.	Direct medical costs	Not stated	-	-	Not stated	-	-	Not stated	-
(2004)	Direct non-medical costs	Not stated	-	-	Not stated	-	-	Not stated	-
8 months	*Total costs - Payers*	*Not stated*	-	-	*Not stated*	-	-	*-€291 (-1427–691)*[c]	-
Chisholm et al.	Intervention costs	€255 (234–282)	-	-	-	€169 (150–186)	-	-	€85 (55–118)
(2001)	Other direct medical costs	-€56 (-226–126)	-	-	-	-€67 (-178–56)	-	-	€6 (-193–225)
6 months	Direct non-medical + indirect costs	-€194 (-1634–1006)	-	-	-	-€375 (-1341–67)	-	-	€180 (-1522–1693)
	Total costs - HCP	*€201 (36–377)*	-	-	-	*€101 (-9–228)*	-	-	*€98 (-65–402)*
	Total costs - Society	*€6 (-1447–1282)*	-	-	-	*-€274 (-1236–639)*	-	-	*€280 (-1509–1720)*

c. The comparison between CBT and SG is not performed since SG is dominated by CBT, i.e. SG is more expensive and less clinically effective than CBT; b. Own computations; c. Mean value and 90% confidence interval; CBT: cognitive behaviour therapy; SG: guided support group; DN: do nothing; GET: graded exercise therapy; CT: counselling therapy.

In Severens et al.,[142] the mean total costs of CBT (€3 104) are higher than those of its comparator (DN: €1 842) from the perspective of the payers (i.e. including direct medical and direct non-medical costs). In this study,[142] CBT was found to result in a mean incremental cost of €1 262 over DN but a confidence interval around this mean value was not reported. It was thus not possible to assess the statistical significance of this result.

When a societal perspective was adopted (i.e. including direct medical, direct non-medical and indirect costs), CBT became cost saving (incremental total costs over DN: - €1 020). Compared to DN, the additional costs of doing CBT (intervention costs of €1 825) are thus largely compensated by the reduction in productivity (indirect) costs. Since no confidence interval was reported, it is however not possible to assess whether this result is statistically significant.

From the perspective of the health care payers (i.e. including only direct medical costs for patients diagnosed with chronic fatigue), the mean total costs of CBT in Chisholm et al.[143] were higher than those of CT. By contrast, with a unit cost for GET (€46.4) higher than the unit cost for CBT (€45.2), McCrone et al.[141] reported that CBT was less expensive than GET from the perspective of the payers. In Chisholm et al.[143] and in McCrone et al.,[141] the incremental total costs of CBT over CT and GET, respectively, were associated with large 95% confidence intervals crossing zero. This indicates that, in both studies, CBT may well be more or less (or even equally) costly than its comparators. Chisholm et al.[143] have evaluated the number of days that patients were unable to work because of their condition and have incorporated the value of the time lost in their economic evaluation. They found that CBT remained more costly than CT, even when a societal perspective was adopted. The confidence interval associated with this mean incremental total cost was however large and included the value zero (€280, 95% CI: - €1 509–1 720).

3.3.2 Incremental health outcomes

Table 10 provides a comparison of the values of the three main health outcomes reported by the studies.

Table 10. Mean and incremental health outcome (95% confidence interval)

Author	Publication year	Time horizon	Mean health outcome					Incremental outcome: CBT vs		
			CBT	SG[a]	DN	GET	CT	DN	GET	CT
Quality adjusted life years										
Severens et al.	2004	14 months	0,074	-0,002	0,046	-	-	0,028	-	-
Mean decrease in fatigue score										
McCrone et al.	2004	8 months	2,7 (-0,6–6,0)	-	-	2,4 (-0,6–5,4)	-	-	0,3	-
Chisholm et al.	2001	6 months	7,34 (5,5–9,1)	-	-	-	8,28 (6,5–10,0)	-	-	-0,9 (-3,6–1,8)
Percentage of patients with a clinically significant decrease in fatigue										
Severens et al.	2004	14 months	27%	11%	20%	-	-	7%	-	-
McCrone et al.	2004	8 months	79%	-	-	73%	-	-	6%	-

a. The comparison between CBT and SG is not performed since SG is dominated by CBT, i.e. SG is more expensive and less clinically effective than CBT; CBT: cognitive behaviour therapy; SG: guided support group; DN: do nothing; GET: graded exercise therapy; CT: counselling therapy.

Based on the positive mean values reported by the studies, it appears that all therapies (with the exception of SG[142]) considered in the economic evaluations improve the health outcome of both CFS[142] and chronic fatigue[141, 143] patients between baseline and follow-up. The degree of statistical significance of this mean improvement is however hard to assess since confidence intervals around the means are either not reported or comprise the value zero.[141]

In Severens et al.,[142] treatment with SG was found to reduce the quality of life of CFS patients from intake to 14 months follow-up (-0.002). This option was thus discarded by the authors as a relevant comparator to CBT. Compared to DN, the gain in QALYs obtained by CBT is small with 0.028 QALYs gained (about 10 days) over a 14 months follow-up.[142] Although no confidence interval was reported, Severens et al.[142] stated that this small advantage of CBT over DN is highly statistically uncertain. Likewise, the percentage of CFS patients with a clinically significant decrease in fatigue was 7% higher in the CBT group than in the DN group but because confidence intervals were not reported, it was not possible to assess whether this small advantage of CBT is statistically significant or not.[142]

Treating chronic fatigue patients with CBT resulted in a mean improvement in the fatigue score of 0.3 units compared to GET,[141] and in a mean deterioration of 0.9 units compared to CT.[143]

Both results did however not show statistical significance since the confidence intervals of the mean changes of CBT and GET largely overlapped (CBT: 2.7, 95% CI: - 0.6–6.0; GET: 2.4; 95% CI: - 0.6–5.4)[141] and since the reported confidence interval around the incremental change between CBT and CT crossed zero (- 0.9; 95% CI: - 3.6–1.8).[143] The clinical effectiveness of CBT, expressed as mean unit change in the fatigue score, may thus well be similar to that of GET or CT for chronic fatigue patients. The percentage of chronic fatigue patients with a clinically significant decrease in fatigue was 6% higher in the CBT group than in the GET group but no confidence interval around this mean value was reported in McCrone et al.[141]

3.3.3 Cost-effectiveness ratios

The studies results are summarised in Table 11 and are discussed below.

3.3.3.1 CFS patients: CBT versus DN

From the perspective of the payers, Severens et al.[142] reported a cost-effectiveness ratio for CBT versus DN of €25 147 per additional patient with clinically significant improvement or €63 250 per QALY gained. The uncertainty around those ICERs was estimated by plotting the results 1 000 bootstrap replications of the incremental costs and outcomes on the cost-effectiveness plane and by reporting the proportion of the dots in each quadrant. From the perspective of the payers, none of the 1 000

replications were found in the lower quadrants, indicating a significantly higher cost for CBT than for DN. CBT further demonstrated a small clinical advantage (whether expressed in terms of patients with a clinically significant improvement or in terms of QALYs gained) over DN since 64% to 78% of the dots were found in the right quadrants. The uncertainty about the cost-effectiveness of CBT over DN remains however high since CBT was thus found to increase the total direct costs at an either better (in 64 – 78% of cases) or worse (in 22 – 36% of cases) clinical effectiveness than DN.

When a societal perspective was adopted, the ICER of CBT versus DN became more favourable with a cost per QALY gained of €26 180.[142] With the inclusion of the productivity (indirect) costs, there is indeed now a probability of 54% that CBT reduces the total costs compared to DN. As for the payers' perspective, CBT also demonstrated a small clinical advantage over DN with 65% of the iterations in the right quadrants. The uncertainty around those results for the society is also extremely high since the dots simulated were almost evenly scattered around the four quadrants of the cost-effectiveness plane.

3.3.3.2 Chronic fatigue patients

CBT VERSUS GET

From the perspective of the payers, McCrone et al.[141] found that, compared to GET, CBT resulted in a non-significant improvement in clinical outcome (expressed in terms of mean decrease in fatigue score) and in a non-significant decrease in total costs (see Table 9 and Table 10). Based on 5 000 bootstrap replications of the incremental costs and outcomes of CBT versus GET, McCrone et al.[141] found that CBT had the highest probability of being the optimal therapy (i.e. of resulting in a higher net benefit compared to GET) for any value of the ceiling ratio. This probability was however only 59% at the ceiling ratio of €0 per patient with a clinically significant improvement (i.e. if society does not place any value on a clinical improvement in fatigue), and at most 76% for any value of the ceiling ratio above €7 540. Higher values of the ceiling ratios did not increase the probability of CBT acceptance over GET since the costs and outcomes of both therapies were very similar.

CBT VERSUS CT

Chisholm et al.[143] found that there is almost neutrality between CBT and CT in terms of incremental costs and change in fatigue score (seeTable 9 and Table 10) so that there is no cost-effectiveness advantage of one strategy over the other, neither from the health care payer nor the societal perspective.

Table 11. Results of the studies

Authors (Publication year) Country	Results			
	Viewpoint	CBT vs	Incremental cost-effectiveness ratio[a]	Cost-effectiveness plane[b]
Severens et al.			***Outcome: Additional patient with a clinically significant improvement***	
(2004)	Payers	DN	€20532 (€25147) per patient with a clinically significant improvement	22% | 78% 0% | 0%
The Netherlands			***Outcome: QALY gained***	
	Payers	DN	€51642 (€63250) per QALY gained	36% | 64% 0% | 0%
	Society	DN	€21375 (€26180) per QALY gained	15% | 31% 20% | 34%
McCrone et al.			***Outcome: Additional patient with a clinically significant improvement***	
(2004)	Payers	GET	Probability CBT is cost-effective at £0 threshold: 0.589 Probability CBT is cost-effective at £5000 (€7540) threshold: 0.766	Not reported
UK			***Outcome: Mean decrease in fatigue score***	
	Payers	GET	Probability CBT is cost-effective at £0 threshold: 0.663	Not reported
Chisholm et al.			***Outcome: Mean decrease in fatigue score***	
(2001)	HCP	CT	Unconclusive results	Not reported
UK	Society	CT	Unconclusive results	Not reported

a. The original figures are first reported. Figures in parentheses are original figures converted to Belgian 2007 €; b. The horizontal axis represents the difference in effect between the intervention of interest (A) and the relevant alternative (O), and the vertical axis represents the difference in costs. Upper right quadrant: A is more effective and more costly than O. Lower right quadrant: A is more effective and less costly than O. Lower left quadrant: A is less effective and less costly than O. Upper left quadrant: A is less effective and more costly than O; CBT: cognitive behaviour therapy; DN: do nothing; GET: graded exercise therapy; CT: counselling therapy

3.4 SENSITIVITY ANALYSES

Besides probabilistic modelling, none of the studies performed any further extensive sensitivity analysis on the cost-effectiveness of CBT versus its comparators.

In Severens et al.,[142] varying the unit costs of a CBT session was found to have a great impact of the total mean incremental cost. Setting the therapist training costs to zero reduced the ICER of €25 147 per patient with a clinically significant improvement to €21 774 from the payers' perspective, and the ICER of €26 180 per QALY gained to €17 737 from the societal perspective.

3.5 CONCLUSION

From this review of the economic literature, it can be concluded that the administration of CBT to CFS patients is a dominant option compared to SG since, based on the reported mean QALYs and total costs from the payers' perspective (in the context of the Netherlands), SG was found to be both more costly and less clinically effective than CBT.[142] Further, the administration of CBT to CFS patients was found to be more costly than DN for the payers', but further resulted in a small clinical advantage over DN. The probability that CBT is more clinically effective than DN was indeed evaluated at 64% to 78%.[142]

A strong limitation to the above conclusions is that they rely on the results of a single published economic evaluation of various treatment options for CFS patients.[142] In view of this limited evidence, ideally other economic evaluations targeting this specific population could be conducted to validate (or refute) Severens et al.'s[142] results.

Concerning treatment of chronic fatigue patients (patients not fulfilling all CFS-criteria), it can further be concluded based on the results of two economic evaluations,[141, 143] that the comparative advantage of CBT against other therapies for the treatment of chronic fatigue patients is extremely weak, both in terms of incremental costs and clinical effectiveness. Neither Chisholm et al.[143] nor McCrone et al.[141] could demonstrate a clear and significant difference in the costs and outcomes of CBT versus GET or CT, suggesting that those therapies may all well be equally costly and clinically effective.

CBT seems however to present a small advantage over GET since the probability that CBT results in higher net benefits than GET varied from 59% to at most 76%.[141]

None of economic evaluations reviewed here (whether targeting CFS or chronic fatigue patients) assessed the cost-effectiveness of the joint administration of CBT plus GET versus a relevant comparator. Though the direct medical costs of administering both therapies to CFS patients will certainly be much higher than those of administering a unique therapy, the potential additional savings in productivity costs and potential additional therapeutic gains of both therapies combined are currently unknown. Therefore, the comparative advantage of a combined CBT plus GET therapy for CFS patients versus CBT or GET alone cannot be estimated.

Given the great uncertainty of the studies' results it appears surprising that, despite probabilistic modelling, not all of the studies report the confidence intervals around their mean and incremental costs and outcomes. This is crucial especially since the 95% confidence interval of the incremental costs or outcomes is expected to show a negative lower bound. Further, in the presence of such uncertainty, the percentage of the simulated results falling in each quadrant of the cost-effectiveness plane should be reported, together with the net benefit function for various values of the ceiling ratio.[150] This was only partly done in Severens et al.[142] and in McCrone et al.[141] Due to their design, RCT-based piggy-backed economic evaluations inevitably present some weaknesses, such as a limited time horizon or a lack of power to demonstrate differences in costs or outcomes (if only a subset of the original RCT population is used for the economic evaluation). This could have been dealt with (at least partly) by the use of modelling.

The uncertainty of the studies results in general hampers to derive any firm conclusion, let alone to extrapolate the results to the Belgian context. The main factors precluding the transferability of the results to Belgium being the relative costs of CBT and its comparators, and the costs CBT treatment, informal care and productivity. These costs are much likely to vary between countries, due to differences in price levels and treatment practices. Another factor precluding the generalizability of the results is the intensity at which CBT and other therapies against CFS are administered in Belgium. The extent to which different intensities of CFS therapies have an impact on the clinical outcomes is however not clear.

Recently, NICE has done such a transferability exercise by running the Dutch economic evaluation of Severens et al.[142] using local UK costs to meet the NICE NHS perspective (i.e. a health care payer perspective). Using the reported QALY difference at 14 months from Severens et al.,[142] they report a mean ICER of £16 036 (€22 251) per QALY gained. No conclusion was drawn from this figure since the ICER was highly dependent on variations in the utility gains.

In short, in view of the limited evidence available about the cost-effectiveness of CBT versus other therapies, the comparative advantage of CBT in terms of costs and clinical effectiveness could not be demonstrated with certainty. For CFS patients in particular, CBT increased the total direct costs at an either better (in 64 – 78% of cases) or worse (in 22 – 36% of cases) clinical effectiveness than DN.[142] For chronic fatigue patients in general, CBT was found to be equally cost-effective as CT,[143] and only slightly more cost-effective than GET.[141] Given the uncertainty associated with those results, the selection of a therapeutic strategy for the treatment of CFS patients is likely to consider other factors, such as the accessibility to health care or the individual preferences of the patients.

Key messages

- **Based on the limited cost-effectiveness evidence available, the comparative advantage of CBT versus other therapies (DN, GET, CT or SG), whether for CFS or chronic fatigue patients, could not be demonstrated with certainty.**
- **The administration of CBT (16 sessions) to CFS patients decreased direct non-intervention (medical and non-medical) costs as compared to DN.**
- **However, including intervention costs significantly increased the total direct (medical and non-medical) costs at an either better (in 64 – 78% of cases) or worse (in 22 – 36% of cases) clinical effectiveness than DN. Including indirect costs turned out to be cost saving (in the context of the Netherlands), although this conclusion was also highly uncertain.**
- **For chronic fatigue patients, the probability that the administration of CBT (6 sessions) is the optimal strategy as compared to GET (i.e. CBT results in higher net benefits than GET) varies from 59% to at most 79%.**
- **For chronic fatigue patients, the administration of CBT (6 sessions) as compared to CT, did not demonstrate any significant clinical or economic advantage.**
- **The evidence about the cost-effectiveness of therapeutic strategies for CFS patients is scarce. New economic evaluations should best use modelling to extrapolate their results.**
- **None of economic evaluations assessed the cost-effectiveness of the joint administration of CBT plus GET versus a relevant comparator.**

4 PROGNOSIS: A LITERATURE REVIEW

4.1 LITERATURE REVIEW

The literature review conducted in the chapter 2 identified a systematic review on disability caused by CFS[20] and another one describing the prognosis of chronic fatigue syndrome.[151] In this last paper, a comprehensive search was undertaken from January 1980 to October 2003. Consequently, we undertook an updating literature search since 2003 to 2008 (see Appendix 1).

The primary search in Medline (search window: 2003-2008) yielded 37 citations and the primary search in Embase (search window: 2003-2008) yielded 63 citations. One reviewer assessed all titles and abstracts identified from the searches of these two electronic databases for potential relevance. Of these, only 5 focused on prognosis in CFS patients and were accepted, one of which being the systematic review aforementioned.[151,65,6,152,153] These five papers were retrieved in full and then assessed for possible inclusion. The paper aiming to distinguish prognosis of different fatigue diagnostic labels[6] was not included according to the lack of clear definition of CFS cases and other methodological biases.

4.2 RESULTS

The systematic review performed by Ganz et al.[20] included 53 studies which described a total of 4 558 patients with CFS; 22 of these studies also described healthy controls (n = 775). Most studies were conducted in North America (n studies = 30; n patients = 1 942). Twenty were performed in Western Europe (n patients = 1 807), and two in Australia or New Zealand (n patients = 65). One study was multicontinental (n = 744). For inclusion in this systematic review, studies were required to use at least one of the four accepted diagnostic criteria for CFS. Among CFS patients, 76% were female. Mean age was reported in 48 studies (n patients = 4 372), and ranged from 24.7 to 46.1 years, with a mean of 38.4 years. Mean duration of CFS in all studies that reported this parameter (n studies = 40, n patients = 3 976) was 5.5 years, and ranged from 1.9 to 8.5 years.

The total number of employed CFS patients was reported in 35 studies (n = 2 652; 42% employed). The number of unemployed patients was reported in 37 studies (n = 2 720; 54% unemployed). Some studies divided employment into full- time vs. part-time, and in these studies, an even greater difference was seen between CFS patients and controls. In 16 studies reporting this measure, only 19% of 967 CFS patients worked full-time, while in two of these studies, 75% of 53 controls worked full-time. None of the baseline demographic, clinical or psychiatric traits (age, gender, marital status, mean duration of CFS symptoms, mean number of years of education, and incidence of depression) have been shown to be consistently predictive of CFS patients' improvement and ability to return to work.

In Cairns et al. literature review,[151] prognosis was described in terms of the proportion of individuals improved during the period of clinical follow-up after diagnosis was made and without systematic intervention (natural course). Return to work, other medical illnesses and death as outcomes were also considered, as were variables which may influence prognosis. Twenty-eight articles met the inclusion criteria and, for the 14 studies of subjects meeting operational criteria for CFS, the median full recovery rate was 7% (range 0–48%) and the median proportion of patients who improved during follow-up was 39.5% (range 8–63%). Recovery rate varied according to duration of follow-up, one study showing 31% recovery at 5 years compared with 48% at 10 years. In five studies, a worsening of symptoms during the period of follow-up was reported in between 5 and 20% of patients.

The secondary care studies reported a median recovery rate of 23.5% (range 2–70%). The median proportion of patients who improved during follow-up was 44% (range 38–64%) in four studies having reported this outcome. There is no evidence that older age and high fatigue severity at baseline would be predictive of a worse outcome as well as there were no clear physical predictors of outcome.

Conversely, a sense of control over symptoms and not attributing illness to a physical cause were all associated with a good outcome. Return to work at follow-up ranged from 8 to 30% in the three studies that considered this outcome. Whereas no significant predictor of return to work was identified, the probability to return to work is lower for those who had a diagnosis of major depression at baseline. Moreover, patients who had been ill for many years and experienced long periods of sickness absence have more difficulties to return to work than workers having short periods of sickness absence.

A prospective study in a clinic-based cohort followed the natural course of a cohort of patients with CFS (n=93) over a 1.5-year period.[153] Approximately 18% of the patients no longer met criteria for CFS at their last research appointment 1.5 years after their index visit. Results of general linear mixed model analyses showed that (estimate [standard deviation], p-value): less education (-0.42 [0.18], p=0.02), being unemployed (1.29 [0.58], p=0.03), worse mental health (-0.05 [0.01], p<0.001), more use of sedating (0.72 [0.28], p=0.01) and antidepressant (0.51 [0.25], p=0.04) medications, and more somatic attributions for their illness (0.65 [0.18], p<0.001) were associated with worse symptom severity over time.

Finally, Darbishire et al. (2005)[152] explored the role of baseline characteristics of 105 patients who presented with fatigue in primary care in determining outcome following either graded exercise or cognitive behavioural therapy. Chronic fatigue syndrome status, i.e. meeting Fukuda's criteria, was the most robust predictor of final fatigue following therapy. While, individually, functional impairment and greater perceived negative consequences add to the power of chronic fatigue syndrome status to predict final fatigue, they add no more power when combined.

According to the report published by the Royal College of Paediatrics and Child Health (2004)[17], there are no paediatric population-based follow-up studies to provide evidence of prognosis. Information on prognosis and prognostic factors comes from longitudinal follow-up of case series, where it is difficult to determine the representative nature of the cases and the effect of responder bias. Most studies only involve few cases, with a variable duration of follow-up both within and between studies, making correlation with care/treatment not possible. Conclusions that could be drawn are that prognosis is more favourable for children than for adults with 60-80% of CFS children partially or completely recover with an average duration of illness of 3-4 years. No studies have reported any death from the condition.

Key messages

- **Three quarters of CFS patients are women, and this disorder is most common in young persons between the ages of 25 and 50 years.**
- **Physical and cognitive impairments experienced by CFS patients are endured for many years (range 2 – 8 years).**
- **More than a half of CFS patients are unemployed or loss their job due to their condition.**
- **Among employed CFS patients, less than 20% work full-time.**
- **There is no evidence that older age and high fatigue severity at baseline would be predictive of a worse outcome.**
- **No baseline demographic, clinical or psychiatric traits can predict CFS patients' improvement and ability to return to work.**
- **However, more somatic attributions for illness are likely to be associated with worse symptom severity over time.**
- **Recovery is most common within the first 5 years of illness. The proportion of CFS patients who fully recover without systematic intervention is low (median rate of 7%) but the proportion of CFS patients who improve is higher (median rate of 39.5%); these proportions increase over time (after 5 and 10 years).**
- **The worsening of symptoms during follow-up occurs in 5-20% of CFS patients.**
- **Patients who had been ill for many years and experienced long periods of sickness absence have more difficulties to return to work.**
- **Prognosis for CFS children and teenagers is more encouraging, with partial or total recovery obtained after 3-4 years.**
- **Measuring outcomes in terms of patients needs (e.g. quality of life, relieving fatigue and pain) and societal needs (e.g. return to employment, fewer expenses devoted to diagnosis and rehabilitation) are both valuable.**

5 PATIENT ISSUES

5.1 METHODOLOGY

In order to identify and describe available information about patients' experiences with the illness, the relationships with others, the healthcare system or the administration as well as their expectations and/or complaints, we explored several approaches:

Firstly, the primary search in PsychInfo yielded 90 references and the primary search in Sociological Abstracts (CSA Illumina) yielded 39 citations (see Search Strategy in Appendix 1). No period restriction was applied. One reviewer assessed all titles and abstracts identified from the searches of these two electronic databases for potential relevance. Of these, 22 focused on CFS patients' experiences with the illness, the healthcare system or the administration and were accepted. These papers were retrieved in full and then assessed for possible inclusion.

Secondly, in February 2008, we have conducted a search on websites developed by patients support groups. The review was broad searching the following websites:

France

- L'Association Française du Syndrome de Fatigue Chronique et de Fibromyalgie : (http://asso.nordnet.fr/cfs-spid/ et http://www.cfs-news.org/francais.htm)

Belgium

- CVS Contactgroep (http://www.cvscontactgroep.be/)
- E.M./ C.F.S. : Association de Belgique E.M. et de la Fatigue Chronique (http://www.me-cvs.be/)

UK

- The ME Association (http://www.meassociation.org.uk/)
- Patient Support Group UK (http://www.patient.co.uk/showdoc/27000752/)
- Association of Young People with ME (http://www.ayme.org.uk/)

The Netherlands

- ME/CVS Stichting Nederland (http://www.me-cvs-stichting.nl/)

Germany

- MCS + CFS – Initiative NRW: Multiple Chemical Sensitivity / Chronic Fatigue Syndrome – Initiative NRW e.V. (http://www.mcs-cfs-initiative.de/index.html)

Québec

- L'Association Québécoise de l'Encephalomyélite Myalgique (http://www.aqem.org/index.php)

5.2 RESULTS

Qualitative studies among CFS patients are available to expose patients' experiences with their illness,[154] their relationships with others[155,156] and coping strategies used.[156] In most studies, qualitative data were obtained from interviews using a guided questionnaire among small sample of patients (5[154], 16[156], 17[157,158] to 25[159]), including men and women with illness duration varying between 1 and 40 years. Studies conducted by Asbring[159,155] only considered women. Analyses used process of thematic analysis,[154] narrative typologies,[158] or grounded theory[159], i.e. only theoretical concepts that coincide with the data are used. Studies were mainly conducted in CFS clinics and the generalisability to wider populations should be made with caution.

Many CFS patients are not all that easy to engage face to face. They are too slow, too tired, too ill and pained.

The internet allows patients to "discuss" asynchronically when they are needed and when they feel better. Based principally on a large archive of internet newsgroup postings, and on fieldwork and published debates, an original article[160] examines how facts are talked about and experienced by CFS sufferers.

5.2.1 Patients' feelings and symptoms

At the onset, patients believed that they had the flu or an acute viral illness and treated the symptoms consequently. At first, the symptoms were tolerated because considered to be linked to an acute illness, having to rapidly recover. Time was taken off from work or school as necessary. The next stage was the realisation that symptoms did not follow the normal pattern for flu or infection, lasted longer than expected and became more severe yet remained non-specific.[157]

Patients may experience daily fluctuations in symptoms of CFS although symptoms remain present and impair functioning. Compared to healthy subjects, CFS patients present higher ratings of fatigue, pain, sleep disturbances and social isolation. Physical fatigue was described in terms of symptoms, such as headaches, nausea, dizziness, muscle weakness, and feeling like one had the flu. Mental fatigue included difficulties with concentration, memory, and processing information.[154] Many also reported not being able to stand emotional stress, bright light, temperature extremes or heavy noise and having difficulty to sustain concentration even to read or to watch television.[132] Aches and pains take many forms, including pains in the muscles and joints of upper and lower limbs, pains in the upper back, headaches, chest pains and breathing problems.[84]

Hypersomnia is common, particularly in the acute stage. Sleep onset difficulties, fragmented sleep, non-restorative sleep, morning exhaustion, and abnormal diurnal variation of sleep rhythms and energy levels are commonly reported.

Patients often reported an incapacity to deal with simple matters, such as filling in a form, or attending the consultation, without becoming exhausted.[84] These symptoms obliged patients to restrict their range of activities and to weightily combine activities and rest periods. Consequently, most of the patients experienced deterioration in work, study, self-care, domestic tasks, relationships, leisure leading to loss of lifestyle, family and friends, support system and self-esteem. Simple daily activities such as driving or travelling, walking and climbing stairs, eating, showering, and watching television were compromised by physical fatigue.[154,157] Patients also contrasted an empty present and desolate future with a past that had promised much until illness destroyed this. Frustrations included the loss of career or plans for this, the loss of income and social contacts.[157,161] Many patients who remained employed had to change jobs, work fewer hours and/or receive less pay for their work since becoming ill. Certain work environments exacerbate symptoms (e.g. repetitive motor tasks, prolonged sitting and/or standing, stressful work environment), and work accommodations may not be readily made.[161]

Pains and fatigue are the main reported symptoms leading to an important discrepancy between patients' perspectives and doctors' perspectives. From the patient's perspective, it is the body that forms the locus of pain; this painful body is the main argument to request treatment and cure. From the physician's point of view, the unrelieved exhaustion is central and involves extensive references to limitations of physical and cognitive functioning.[84]

Patients considered that the term CFS is misleading as too general, belittled and marginalized by others including caregivers. While The World Health Organization (WHO) classifies CFS as a neurological illness (G93.3), NICE has failed to accept this conclusion, considering that to do so did not reflect the nature of the illness, and risked restricting research into the causes, mechanisms and future treatments for CFS.[2] The ME Association (a UK patient-support association) was dissatisfied with this decision leading to a 'one size fits all' approach to management. Moreover, a relaxation of the clinical criteria for defining CFS - the NICE redefinition requiring only one of the minor symptoms - would bring in more people with undiagnosed chronic fatigue under the ME/CFS umbrella. This would complicate the picture still further.[162]

5.2.2 Patients relations with others

5.2.2.1 Social relations

CFS patients, among them a lot of women, felt they were stigmatized. Firstly, their moral characters were called into question due to the absence of visible external signs of the illness and negative diagnosis tests. Many patients believed that evident external symptoms would have enhanced their credibility. Moreover, the diagnosis, difficult to establish came in some cases very late. The contacts with the social insurance office, for example, were often experienced as problematic (nonchalance and doubt about patients credibility and moral attitude) due to the condition not yet having been verified with a diagnosis. Patients felt being accused of lying about their distress and trying to avoid their duties, especially in relation to work.[155]

A lot of patients experienced a significant decrease in their social life and in time spent in recreational activities or hobbies. CFS patients often lost friends and the support of their family. Decreased social and recreational functioning may be associated with high rates of mood disturbances.[161] In some cases, illness was described as a reason for divorce or separation with family members.[159]

5.2.2.2 Relations with doctors and other caregivers

PATIENTS' POINT OF VIEW

In Schoof's study, interviewees indicated how many healthcare providers lacked knowledge about their condition or did not believe in. They were really frustrated when healthcare providers were uninformed.[156]

Patients also expressed that their credibility had been questioned by the caregivers, in particular by doctors, often after tests and other examinations did not indicate any pathological problems.[154] While doctors were positively disposed prior to the test results, they adopted sceptical attitudes when negative test results were received. Some doctors, in advance and without having carried out proper examinations, categorized patients' problems as fictitious or related to psychological reasons,[155] thinking patients were lazy or irresponsible.[156]

Moreover, sufferers described their experiences of being denied healthcare and legitimacy through bureaucratic categories of exclusion as dependent upon their lack of biological facts.[160] In USA, the American biomedical system demands disease categories (International Classification of Diseases) before compensation, and diagnosis before treatment. Consequently, without codes, people are at risk to be abandoned out of reach of any social safety net. Without clear definition, insurance companies, for instance, can recategorize illnesses arbitrarily as physical or mental, with the advantage to them that they can pay less for classified mental illnesses.[160]

In UK, a study conducted among CFS patients referred to a specialist clinic reported that two-thirds of all interviewees (N=68 patients) were dissatisfied with the quality of care they received.[163] These patients described delay and confusion over diagnosis. Whereas patients attributed their symptoms to a physical cause, doctors believed CFS to be psychological or even psychiatric. Such disagreement led to dissatisfaction over diagnosis and treatment. Patients considered medical advices consequently inadequate or conflicting and felt doctors dismissive, sceptical or openly disbelieving.[163] Even in the patient support literature, patients considered the mention of psychiatric disorder as a dismissal of their complaints.[84]

PHYSICIANS' POINT OF VIEW

Asbring and Närvänen studied physicians perspectives on CFS patients.[164] They interviewed 26 physicians who all had some experience of either CFS. Firstly, physicians emphasized the distinction between a disease and an illness. They expressed scepticism for conditions characterised by a lack of objective measurable values that would make it possible to establish the cause of the condition, i.e. which cannot be characterised as a disease. CFS which cannot be verified from objective measurable values was defined as illness and thus considered as less threatening than health problems with disease status. CFS symptoms were viewed by physicians to be ones that can be lived with.

According to interviewees, CFS patients had not previously experienced more severe conditions and often exaggerated the severity of their problems. Secondly, physicians considered that there was a discrepancy between how CFS patients expressed their symptoms (fatigue and pain) and how a sick person, according to their personal point of view, is expected to look and behave. To be accepted as a sick person, appearances seemed to be really important. Consequently, they felt doubtful about the veracity of the patient' condition; patient' morality is actually called into question particularly to decide if a patient has to put on the sick list.[164] Particularly, several physicians expressed hesitation about setting the diagnosis (CFS) afraid that the patients may become too illness-fixated.

Physicians themselves viewed CFS patients as showing scepticism regarding the physician's knowledge of their condition and the possibilities of doing something for them.[156]

This perception was confirmed in a larger postal survey addressed to 1 054 GPs in UK (number of respondents = 811),[165] where only 49% of respondents correctly identified key clinical features of CFS and 63% of GPs selected either these key features or other most frequent clinical features. Among respondents, 28% of GPs did not accept CFS as a recognizable clinical entity and adopted less positive attitudes towards patients than GPs who accepted CFS a real entity. Only 12% of GPs enjoyed working with CFS patients.[165] Even when doctors recognise psychological or social factors, they do not automatically consider referral for mental health interventions because they are unfamiliar with the interventions or think them unavailable or unnecessary.[166]

5.2.3 Coping strategies

5.2.3.1 Withdrawal

A withdrawal is a strategy to avoid the demands and expectations of other people. Particularly, patients tend to avoid people who had reacted negatively to them and their illness. They compensated for the avoidance of certain people by a greater intimacy with, and closeness to, others. Some patients also withdrew from social life when they could not cope with meeting people or participating in various activities due to fatigue and poor health or found it difficult to plan activities in advance when their condition was unpredictable from one day to the next.[155,159]

When patients felt that they were called into question by doctors or caregivers, they hesitated to seek care or waited as long as possible before contacting them again, preferring to turn to caregivers within alternative medicine.[155]

5.2.3.2 Concealment

Another strategy used by patients to manage their situation is to try to participate in social life instead of withdrawing from it, by concealing the illness, and act as a happy, healthy, and normal person, only to almost collapse later when they arrive home. Another strategy leads to controlling information and not telling others about the illness, in order to diminish the risk of stigmatization and to maintain a desired identity. An inverse way of managing the situation is to actively spread information about the illness to colleagues, friends, and closest family members.[155] Many sufferers try to educate others, including their doctors through facts. They use the internet to share tips, medical articles, and strategies for making their doctor understand their condition.[160]

5.2.3.3 Communication with other sufferers

A lot of social movements emerge to help and support CFS people. These illness movements have websites and Usenet discussion groups. Usenet is a global, decentralized, distributed internet discussion system. Users read and post public messages (called articles or posts, and collectively termed news) to one or more categories, known as newsgroups. Usenet resembles bulletin board system.

The postings are public commentary with no access restrictions and are most similar to online web logs (or blogs).

Collective sharing of useful information helps people who are otherwise isolated and have to face institutions on their own; patients are thus empowered to navigate the Websites of courts, insurance agencies, mass media, and government.[160]

Collective patient action responds by developing counter-tactics to exclusions. A common topic of discussion on and off the internet concerns how a sufferer should approach his or her doctor to be credible and listened. For example, there are explicit instructions available for how to dress, what to say, what articles to bring and so on. Patients are thus committed to express alternative personal narratives, strategies for surviving, and emotional support.[160]

5.2.3.4 Symptoms management

People prioritise their activities, choosing to undertake some activities and to abandon others. The objective is to maximise the activities they are able to undertake in order to maintain socialisation in areas felt to be valuable.[158] This structure in the activities is imposed by own experiences of relapses following over-exertion.

Patients are searching in a lot of directions to find adequate treatments able to relieve fatigue and pain. In the study conducted by Whitehead in UK among 17 CFS patients,[157] the use of alternative therapies was widespread. Everyone in the group had tried a form of complementary/alternative medicine, many several therapies such as diets (e.g. wheat free, sugar free, no meat, no diary products, high potassium diet), acupuncture, and relaxation. The high use of such therapies was considered by the author as not surprising according to the difficulty to access to specialist care.

5.2.3.5 Treatment

CBT AND GET

The ME Association (a UK patient-support association) was disappointed by the NICE guidance proposing that everyone with mild or moderate ME/CFS should be offered cognitive behaviour therapy (CBT) or graded exercise therapy (GET) as a first choice treatment - regardless of their clinical presentation or the stage of their illness.[162] This association emphasized that the evidence base for both of these behavioural therapies remains weak while treatments remain costly. If everyone with mild to moderate ME/CFS had to be treated with a course of 12 to 16 sessions, a lot of properly trained therapists will be needed as well as extra-money to cover expenses.

Many patients find that their experience of CBT is affected by the therapist's own beliefs about CFS or whether they have any history of working successfully with other patients. For example, if a therapist believes that CFS is little more than tiredness and lack of physical fitness, they may set an aggressive rate of activity programme that is too hard or fast for the patient to follow and does not encourage patient feedback. This inflexible approach may lead to patients ignoring significant warning signs from their bodies, such as seriously increased symptoms. If this is applied in conjunction with the psychotherapy, part of the treatment teaching patients that it is their own thoughts and behaviours that are preventing them from achieving the physical programme, patients may end up believing that they are failing to do the set activities because they are not trying to hard enough, or that they do not wish to get better. Or if the therapist believes that CFS is purely the result of negative thoughts, stress and unhelpful behaviours, then their CBT techniques may turn out to be too confrontational, which may lead the patient to feel blame for their illness. 'No pain, no gain' rarely works for CFS, and all CBT therapists may not be aware of this, especially if they haven't worked with CFS before. It is vital for that a partnership exists between therapist and patient, as CBT depends heavily on trust. A patient needs to be able to trust his therapist to challenge him/her but not push him/her too fast, otherwise s/he may be unable to lose his/her fear of trying something new. Therapists need to take time to understand patients' individual limitations in order to set appropriate goals. Ultimately, patients need to feel like a partner in determining how and when their activity is increased (or decreased in the case of set back) (source: http://www.ayme.org.uk/).

5.2.4 Propositions from patients to better management

- Education: Improving doctors information by including CFS in medical doctor's programs.[156]
- Doctors' behaviour: healthcare providers should take CFS patients seriously, admit what they don't know, study to find out what helps patients, and be willing to treat individuals uniquely, listen to patients, and learn from them. Healthcare providers should help the patient understand that there is no cause and no cure and they must learn to live with it. They must be partners with the patients in healthcare provision. Additionally, healthcare providers should not rely solely on diagnostic tests in making decisions about the illnesses.[156]

5.3 PATIENTS ASSOCIATIONS

Patients associations provide information, support, education and training. They benefit healthy volunteers, people with CFS, professionals and all others interested in the illness.

These associations provide information and support on CFS to people with CFS, their parents, carers, health professionals, partners and many others, striving to develop professional and quality information materials and services. They propose leaflets, books, magazines or newsletters which cover research news, and keep members up-to-date with medical and scientific developments. Particularly, they summarized results from new clinical trials, especially if significant contributions were made or adverse effects were observed (therapies or medicines). Some associations have developed and printed leaflets devolved to social services, educators and employers but also to mass media. Sometimes, they organize conferences to health care professionals, and continuing education programs. Others try to raise funds in order to sustain research activities.

All associations propose Usenet discussion groups and regularly propose activities and meetings. In most cases, associations present a clear message concerning medical advices. They refuse to offer medical consultations and to take over the management of patients' problems. They propose rather counselling services to help patients with healthcare system (e.g. 'How to handle hospital meetings'), with administration to apply for benefits or to obtain disability living allowance. Associations in UK also propose specific devices to help people to dress, to take a bath or a shower, cushions to relieve back pain, and so on.

5.3.1 Patients associations in Belgium

A national association for CFS patients was created in Belgium with two sub-groups, one for Flemish patients who has more than 2 000 members, the other for French patients. The main aims of this association are to make the public and physicians aware of the problem of chronic fatigue syndrome by spreading information, and to help patients with specific problems. To support patients, the association has a call center and a library that gathers all relevant documentation. This association also supports scientific research on causes and pathological mechanisms of this pathology.

Its Website (http://www.me-cvs.be/) proposes summarized information about definition, epidemiology, diagnostic and therapeutics which were tested in clinical trials (without differentiating effective and non-effective treatments).

Key messages

- **Due to their disabling symptoms, patients are obliged to restrict their range of activities leading to deterioration in work, study, self-care, domestic tasks and social relationships;**
- **Patient's perspective of CFS (painful body) differs from physician's point of view (unrelieved exhaustion) leading to conflict regarding appropriate treatment and management strategy;**
- **Coping strategies include withdrawal (from social and working life), concealment (forcing to participate in social life instead of withdrawing from), and communication with other sufferers;**
- **Patients experienced being denied healthcare and legitimacy through bureaucratic categories of exclusion as dependent upon their lack of biological facts;**
- **Physicians expressed hesitation about setting the diagnosis (CFS) afraid that the patients may become too illness-fixated; they do not automatically consider referral for mental health interventions because they are unfamiliar with the interventions or think them unnecessary;**
- **Patients are searching in a lot of directions to find adequate treatments including alternative therapies, diets, acupuncture, and relaxation;**
- **Patients' experience with CBT is affected by the therapist's own beliefs about CFS and effectiveness of CBT; success of the therapy also depends of the partnership established between the therapist and the patient;**
- **CFS associations provide information and support to people with CFS, striving to develop professional and quality information materials and services. All associations propose Usenet discussion groups to help patients to communicate with other sufferers.**

6 BELGIAN DATA

6.1 INTRODUCTION

In 2000, a Working Group of the Superior Health Council formulated problems existing in the care of CFS-patients in Belgium[g]. Four main domains were mentioned:

- Costs for patients as well as society were important;
- CFS patients were threatened by an inconstant social situation;
- CFS patients suffered by the lack of recognition of the medical world, probably due to a lack of consensus on the disorder;
- Working conditions were often maladjusted to the reduced capacities of CFS patients.

Following this report, the Minister of Social Affairs, F. Vandenbroucke, asked the RIZIV/INAMI to establish rehabilitation agreements for CFS reference centres. From April 1st 2002 on, four reference centres for adults and one for children were started up.

In 2006, an evaluation report describing the activities and patient outcome of the reference centres was published[167] by the RIZIV/INAMI Akkoordraad[h]. This report will be summarized in the section 6.2, and will be the main reference for the Belgian data on CFS.

The reason for this is that other forms of care for these patients are difficult to trace: medical diagnosis in ambulatory care (e.g. consultation of general practitioner or medical specialist; ambulatory physiotherapy) is not routinely registered in Belgium; and hospital registration is according to the ICD-9-CM, which does not yet include "Chronic Fatigue Syndrome" as a medical diagnosis. Psychotherapy in private practice is not reimbursed by the national health insurance, and even more difficult to trace; whereas psychological support in "Centra voor Geestelijke Gezondheidszorg/ Services de Santé Mentale" is not organised by the Federal State but by the Flemish/Walloon/Brussels Region.

However, additional information was obtained from the RIZIV/INAMI (Dienst voor Uitkeringen) on the number of Belgian CFS patients that currently receive a support under the Disability Scheme, and on the budgets allowed to the reference centres by the RIZIV/INAMI (see section 6.3.).

6.2 SUMMARY OF THE RIZIV/INAMI REPORT (2006)[167]

6.2.1 Reference centres: tasks and financing

In the starting phase of the reference centres, a link to University hospitals where knowledge on the CFS syndrome was more readily available and research could be performed, was preferred.

The main tasks of the five CFS reference centres (four for adults and one for children) started up from April 1st 2002 on, are (RIZIV/INAMI report p 3– p 61):

a. to give advice on diagnosis of possible CFS patients which are too complex to be diagnosed by the first and/or second line services;
b. to provide time limited therapy for CFS patients that are difficult to treat by the first and/or second line services, or in case it is not clear how the patient should be treated. The therapy should be evidence-based, i.e. CBT and GET are to be included. Patients should be referred back as soon as possible;

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g Ministerie van Sociale Zaken, Volksgezondheid en Leefmilieu. Hoge Gezondheidsraad, onderafdeling I.2 "Psychosociale aspecten van ziekten". Aanbevelingen betreffende de medisch-sociale, economische en juridische aspecten voor patiënten met het syndroom van chronische moeheid. Juli 2000.

h Akkoordraad in het kader van de revalidatieovereenkomsten inzake tenlasteneming door Referentiecentra van patiënten lijdend aan het Chronisch vermoeidheidssyndroom (RIZIV/INAMI)

c. to offer interdisciplinary services, providing a coordinated and patient-centred approach; the diagnostic services should be on an ambulatory basis;

d. to inform, support and teach first and second line services on CFS, so as to make future organisation of most of the care for CFS patients on the first and second level possible under coordination of the patient's general practitioner. In this way, affordable services should be offered to CFS patients, as close to their living places as possible;

e. to advise the RIZIV/INAMI on how to organise this care in an affordable way in the first and second level in the future.

Financing of the system includes four "forfaits" (lump sum):

- a lump sum for the initial multidisciplinary evaluation of the centre;
- a monthly lump sum for the interdisciplinary rehabilitation; which can be paid maximum 6 times during a time period of maximum 12 months;
- a lump sum for a general practitioner (GP) attending his patient's rehabilitation session ("GP participation session")
- a lump sum for a team member attending a meeting of GPs organised by one of the patient's GP ("team member extra muros participation session")

For each of the reference centres, a "normal" patient capacity is agreed on; centres can go beyond their normal capacity but at a reduced tariff. The normal yearly capacity for the four adult centres together is 407 full rehabilitation programs (407 times six monthly lump sums for interdisciplinary rehabilitation); it includes 18.25 FTE (full time equivalents). For the children's centre, the normal yearly capacity is 36 full rehabilitation programs, including 1.75 FTE.

6.2.2 Reference centres: general organisation

Patients should be referred by a medical doctor, a standard referral form should be filled out including demographic, medical and (psycho-)social information, and information on the professional situation of the patient; results of diagnostic evaluations should be included.

A first outpatient consultation by a medical specialist in internal medicine (for the children <18 years: paediatrician) should avoid that patients who clearly don't fulfil the CFS diagnostic criteria (CDC criteria, Fukuda 1994; adapted for children[17]), remain unnecessary on a waiting list. Next, a multidisciplinary evaluation by a psychiatrist, specialist in internal medicine (for additional diagnostic evaluation if necessary) and a rehabilitation specialist as well as other team members take place. For the children, this evaluation is performed by a child psychiatrist, a paediatrician, a master in educational sciences and a physiotherapist. A definite diagnosis is worked out, and psycho-diagnostic data using a semi-structured interview and questionnaires are gathered. Maximal or sub-maximal physical capacity, according to the patient's possibilities, is measured.

Based on this multidisciplinary evaluation, a therapeutic program is proposed to the patient and communicated to his GP. This program can take place at the first or second care level, or at the reference centre itself.

In the last case, re-evaluation takes place at the end of the program, and the reason why the program is finished is noted. Re-evaluation is repeated at 6 and 12 months' follow-up.

Since evaluation of the centres' activities and of the patients' outcome was estimated to be important during the starting years of the reference centres, especially because knowledge on organisation of care for CFS largely was lacking, a general registration system[167] was agreed on, and administrative support for the registration was provided to the centres.

6.2.3 Reference centres for adults: evaluation of results.

The four reference centres were evaluated for the period of April 1st, 2002 till December 31st, 2004.

After an initial starting phase, all three Dutch speaking reference centres reached their normal yearly capacity, and even their maximal capacity, so that long waiting lists were created. The French speaking reference centre reached only 50% of its normal capacity. For all 4 centres, only rarely services were not provided ambulatory, although inpatient treatment is possible according to the RIZIV/INAMI agreement.

6.2.3.1 Adults: Diagnostic phase

Between April 1st, 2002 and December 31st, 2004, 1 655 patients entered the reference centres for the first outpatient consultation. After this first consultation, 94% of the patients seen were considered to be a possible CFS-patient[i]. In 96% of these patients (N=1 087), the diagnosis was confirmed after the multidisciplinary evaluation. According to the RIZIV/INAMI report, an explanation for this high number could be that 64% of the referred patients indicated that they had already been treated before for CFS. Another explanation could be that GPs and second-line medical specialists are highly competent in making the diagnosis of CFS. However, it should be noted that 84% of the referring medical doctors only referred one patient.[j] The average age of the patients who were diagnosed with CFS, was 40 years 8 months; 41% of the patients were between 40-49 years old. The average duration of the fatigue was 4 years 10 months, and 38% of the patients were already fatigued for more than 5 years. About 87% were female, and 10% of the CFS patients had at the time of initial evaluation a full-time and 14% a part-time job. About 26% stated to have some income out of own professional activities; 39% had a partner with an income, and 54% had a sickness allowance.

The diagnostic phase in the reference centres (first outpatient consultation followed by multidisciplinary evaluation) took a long time: 4 to 5 months between first consultation and start of the rehabilitation treatment. It should be mentioned, that in 3 of the 4 adult centres, the first outpatient consultation already comprised an advice by a medical specialist in internal medicine as well as a psychiatrist. This seems an overlap with the next phase of the evaluation, namely the multidisciplinary team "bilan".

Of the patients with confirmed diagnosis of CFS (N=862), 79% were considered to be candidates for an interdisciplinary rehabilitation program in the reference centre. For 30%, advice and education of the patient and/or his caregivers including first- and second level professionals, was proposed (additionally). At least 25% received a special referral to the physiotherapist, for 60 sessions at a reduced tariff ("F-list"); this could be after the interdisciplinary treatment was finished. It should be noted that all centres organised general educational sessions for family and relatives, although for this activity no reimbursement had been foreseen.

6.2.3.2 Interdisciplinary treatment of adults: characteristics and outcome

The interdisciplinary treatments at the reference centres that were finished before January 1st , 2005, comprised on average per patient 41 to 62 hours of rehabilitation, spread over 6 to 8 months (and in one centre 12 months), depending on the reference

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i Between the first outpatient consultation and the end of the multidisciplinary evaluation, 433 patients (28%) dropped out. Since 94% of initial referrals seen at the first outpatient consultation were considered "possible" CFS, of which 96% was confirmed to be definitively CFS, about 90% of the initial referrals (seen at the first outpatient consultation) were definitively diagnosed as having CFS.

j In the postgraduate thesis "Het profiel van de arbeidsongeschikte CVS-patienten en de revalidatie in de CVS-referentiecentra",by Annemans S, Cock I, Nackaerts S, Smets T, Milants P, Verwerft E (2007), under supervision of Donceel P all persons registered in the Turnhout region of the CM (one of the main Belgian sickness funds), were checked for longstanding unemployment; among those persons 153 unemployed CFS patients were found and further analyzed. Of these 153 CFS persons, 73 had been taken care of before, in one of the CFS RCs. According to Annemans S et al, several of these 73 persons suffered from a severe psychiatric comorbidity, i.e. bipolar disorder, vital depression, anorexia or boulemia, and should have been excluded. No numbers were given.

centre. One session lasted 1 hour to 1 hour ½. The largest part of the rehabilitation (50%) was provided by physiotherapists; 37% was provided by psychologists. Psychiatrists and rehabilitation specialists provided respectively 3.6% and 4.2% of the rehabilitation, and social workers 3.2%. For each 30 days of rehabilitation provided, an average of 6.4 group interventions (83%) were provided, and 1.2 individual interventions (17%).

For all 4 centres together, only twice had a general practitioner attended a rehabilitation session of his patient and only once had a lump sum be paid for a team member attending an extra muros GP conference (however, some teaching activities were organised without claiming the lump sum).

89% of the rehabilitation interventions in the centres were stopped because of "end of the RIZIV/INAMI reimbursement period"; for 71% of the patients the team estimated that the maximal result for the patient had been reached, although no patient was considered to be totally cured. Only 2.8% of the treatments were stopped by the patient, who generally speaking seemed very motivated to follow the therapy.

Subjective complaints, quality of life, psychological co-morbidities, physical capacity and employment status were evaluated extensively at the beginning and at the end of the treatment period, and after respectively 6 and 12 months follow-up. For the full list of outcome instruments, and for the statistical tests used, see the RIZIV/INAMI document.

Although drugs used by the patients in the four centres had been registered, only general information on this part of the therapy is given in the evaluation report.

The systematic outcome registration in the four centres revealed that the main complaint of the patients, their fatigue, had improved significantly at the end of the therapy and 6 months later.

Results concerning the patients' quality of life were conflicting: for one group of patients there was a significant improvement as compared to the start of the therapy, for another group of patients this could not be confirmed. However, for all patients the average quality of life was still below the level of healthy adults.

At the beginning of the rehabilitation, many patients presented with psychological problems or psychiatric co-morbidities (e.g. depressive feelings, somatic complaints, anxiety etc). Their average outcome fell outside the range of healthy adults, but did not reach the level of an average outpatient psychiatric population. Although at the finish of the treatment they were improved, their results on psychological evaluation were still outside the normal range.

Physical capacity (maximal or sub-maximal according to the patient's possibilities) did not change between start and end of the treatment.

Employment status decreased at the end of the therapy, from an average of 18.3% of a 38h- working week, to 14.9%. However, it should be noticed that this was not one of the preset goals of the interdisciplinary treatment, and that no specific occupational rehabilitation was foreseen. The percentage of patients living from a sickness allowance increased slightly from 54 to 57%.

6.2.4 Reference centre for children: evaluation of results

The reference centre for children was also evaluated for the period of April 1st, 2002 till December 31st, 2004.

Although it had been estimated that in Belgium about 8 000 children would suffer for CFS, the centre never reached its normal capacity (36 full rehabilitation programs yearly); it reached only 40% in 2004.

100% of all patients seen in the first mono-disciplinary outpatient consultation, were estimated to meet criteria for "possible" CFS syndrome (N=56). After thorough diagnostic evaluation, only 37%, or 19 patients, got a definitive diagnostic label of CFS, because of uncertainty about the diagnostic definition for children and because the team tried to avoid this "label", for which no aetiology or definite cure exists. Fourteen of these patients started interdisciplinary treatment in the centre. For children, the centre

aimed to organize this treatment as much as possible in the children's home environment, in collaboration with local services and the school.

Children generally improved more than adults, as has been described in the literature (see chapter 4). However, due to the small number of participants, no statistical calculations were performed.

It should be mentioned that in 1999, the rehabilitation centre "Zeepreventorium" in De Haan, specialized in residential rehabilitation for children and adolescents (e.g. mucoviscidosis, asthma, obesitas) also started residential rehabilitation for adolescents (12-18 years) suffering from CFS. Only patients not able of following ambulatory rehabilitation in their own neighbourhood are accepted. The maximal treatment duration, provided by a multidisciplinary team, is 6 months. By the end of April 2008, 38 CFS adolescents had been treated.

6.2.5 Belgian CFS reference centres: conclusions and discussion

6.2.5.1 Adults

Based on available epidemiological data for other countries, it can be estimated that about 20 000 Belgian adults suffer from CFS.

Between April 1st, 2002 and December, 31st 2004, 1 655 patients entered the reference centres, but in three centres, long waiting lists exist. For more than 90% of the patients, the diagnosis of CFS was confirmed. Most referred patients had been fatigued since a long time (average of 4.10 years), and had psychological problems or psychiatric co-morbidities, although the level of an average outpatient psychiatric population was not reached[k].

Approximately 80% of the CFS patients followed an interdisciplinary program in the centre; the time between initial outpatient consultation and start of the rehabilitation was on average 4 to 5 months. A solution should be found for this long time period, as well as for the overlap in service between the first outpatient consultation and the multidisciplinary team "bilan" (evaluation).

Although the referring medical doctor was informed by phone or letter, as usual among physicians, very few other initiatives to develop a collaborative care for the patient between the first or second line and the reference centres, were explored. One of the initial aims of the project, to develop a three-level system in which many or even most of the patients would be treated in the first or second level, as close to their living place as possible, was not reached. It is clear that other pathways should be tried out to reach this goal.

Treatment was ended in only 2.8% of the cases by the patient himself, so the motivation of the patients for the treatment seemed to be high. In 71% the team considered the patient to have reached his maximal capacity — although no patient had been cured. Therapy provided systematically included CBT and GET. After treatment duration of 41 to 62 hours of rehabilitation per patient of which 83% group based, spread over 6 to 12 months, patients' subjective feelings of fatigue were improved, but results concerning quality of life were equivocal. Psychological problems or psychiatric co-morbidities improved, but still fell outside the range of healthy adults. Physical capacity did not change; employment status decreased at the end of the therapy. It is difficult however, to judge these results, since no control group had been included.

6.2.5.2 Children and adolescents

A limited number of children has been seen or treated so far, and the capacity of the children's team is not yet reached. The children's team provided an integrated service, directly in the child's own environment as much as possible. Apart from this ambulatory service, residential treatment for adolescents (12-18 years) is possible in the children's rehabilitation centre "Zeepreventorium" in De Haan (Flemish region).

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k According to Prins et al. (2005), no difference in CBT treatment outcome could be found in a group of 270 CFS patients between those patients with and those without psychiatric comorbidities.[93]

Research on treatment for adolescents and children is much more limited than research for adults. Only in 2007 (NICE guidelines), a clear proposal has been agreed on for time duration of fatigue before a definitive diagnosis can be made (3 months). No scientific validation is underpinning yet this proposal. It is generally agreed on that prognosis in young persons is much better.

More research is necessary, before conclusions on structure and organisation of care for children and adolescents can be made.

6.3 OTHER BELGIAN DATA

As already discussed in the introduction to this chapter, data on Belgian CFS patients not diagnosed or treated in the reference centres are difficult to obtain. Nevertheless, some additional information could be obtained.

6.3.1 Belgian CFS patients receiving a support under the Disability Scheme

Data were obtained from the Federal Service for Disability Allowances, part of the RIZIV/INAMI[l].

According to the most recent data available (June, 30th, 2007), 237 999 Belgians were qualifying for a Disability Allowance. Of these persons, 2 171 persons (0.9%) were registered as CFS patients (506 men, 1 665 women). It should be taken into account that this is only estimation, and deducted from the Disability appliances, since no ICD-9-CM code for CFS exists.

6.3.2 RIZIV/INAMI expenses for the reference centres

On May 20th 2008, the RIZIV/INAMI provided the booked expenses and maximum budgets foreseen per year (total for all reference centres in Euro). As shown in Table 12, so far the maximum yearly budget has not been reached yet. Remarkable is the fact that the expenses increase especially for the "bilans" (initial multidisciplinary evaluation).

According to the KCE experts (see colophon) this might be due to the fact that the number of referrals increased, especially since 2005-2006. Since waiting lists were growing, the Akkoordraad (see Introduction) asked the reference centres to focus especially on confirming/rejecting the diagnosis by the initial evaluations. The reference centres probably also could yet rely on the network they had built up to refer patients back to their home environment for rehabilitation. Also, the experts had the impression that more persons were referred not for rehabilitation, but rather for diagnostic confirmation to receive reimbursements, to prove their diagnosis in a lawsuit, etc.

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l Vanwynsberghe Lutgarde, M.D., inspector of the Federal Service for Disability Allowances; dd. March, 27th, 2008.

Table 12. RIZIV/INAMI expenses CFS Reference Centres

All Centres	**2002**	**2003**	**2004**	**2005**	**2006**	***2007****
Total Bilan (Euro)	74 204	420 979	404 689	482 245	531 946	576 238*
Total Rehabili-tation (Euro)	30 404	496 093	683 962	729 612	650 648	494 710*
Total (Euro)	104 608	917 072	1 088 651	1 211 857	1 182 594	1 070 948*
Maximal Expenses limited to (Euro)	Start Up	Start Up	Start Up	1 543 367	1 622 250	1 649 858

*preliminary results (May 2008)

6.3.3 Other Belgian data: conclusion

The data taken into account in the RIZIV/INAMI report (2006) largely rely on data from the reference centres between 2002 and 2004. Since then, it seems that a shift towards a more important diagnostic function is taking place.

7 ORGANISATION AND FINANCING OF CFS CARE IN OTHER COUNTRIES

7.1 INTRODUCTION

When concepts of patient care are developed, each country has to take into account its own specific context due to variables in local circumstances, legislation, or cultural concepts, which all influence the way in which care to patients is or can be provided. Nevertheless, it is worthwhile to study the experience of other countries in management of CFS patients: it can deepen our understanding of organizational, administrative and financing policies and it can lead to new options for care organization.

First, to support the comparative description of care for chronic fatigue syndrome (CFS) in all investigated countries, an organisational model of care for this patients' group was looked for in scientific and grey literature sources (see 7.2)

Next, a questionnaire was developed and the 5 countries that would be investigated were selected (see 7.3). The questionnaire was sent to contact persons in these countries, and the returned information was summarized for each country (see 7.4 to 7.8). A comparative table of the described countries including Belgium was made, and conclusions were drawn (see 7.9).

7.2 A MODEL OF CARE ORGANISATION FOR CHRONIC CONDITIONS

7.2.1 Organisation of care for CFS: a Model for Chronic Conditions

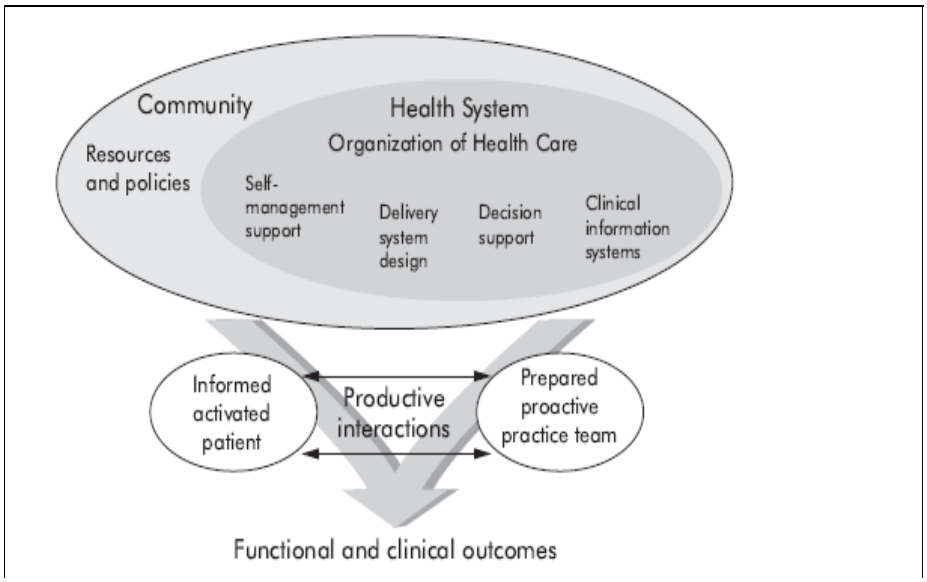
In December 2007, CRD-databases, Medline (PubMed) and grey literature sources were searched for evidence on organisational models proposed to take care for CFS patients (for search strategy, see Appendix 1). However, evidence on this topic is scarce and no description of an organisational model for CFS was found. Alternatively, the same databases and sources were searched for existing organisational models for chronic conditions as a whole (for the search strategy, see Appendix 1). Models for geriatric care were not taken into account, since the typical CFS population is of a much younger age.

Three organisational models were found: the Chronic Care model,[168] the ICCC framework (Innovative Care for Chronic Conditions, WHO 2002), and the New Zealand Chronic Care Management Programme.[169]

Finally, studies discussing the outcomes of Disease Management Programs in chronic disorders were also found.

7.2.1.1 *The Chronic Care Model*

Figure 2. The CCM or Chronic Care Model[170]



The Chronic Care Model (Figure 2) has been developed and described by Wagner, in 2001.[168, 170] The CCM is made up of six major elements: community resources, the health care system surrounding the provider organization, patient self-management, decision support, delivery system redesign, and clinical information systems.[171] In several countries, this model has been used to describe, introduce or study changes in the care of chronic conditions, e.g. Chronic Obstructive Pulmonary Disease or diabetes.[171,172, 173,174-177] A brief, validated patient self-report instrument, the Patient Assessment of Chronic Illness Care (PACIC), exists which assesses the extent to which patients with chronic illness receive care that aligns with the Chronic Care Model (this care should be patient-centred, proactive, planned, and should include collaborative goal setting/problem-solving and follow-up support).[178] In 2005, a meta-analysis assessed whether CCM interventions improved outcomes for specific chronic illnesses. It was concluded that clinical outcomes, processes of care, and to a lesser extent quality of life, were improved in patients receiving at least one element of the CCM; but these findings might not be reliable given the limitations in the review methods.[179]

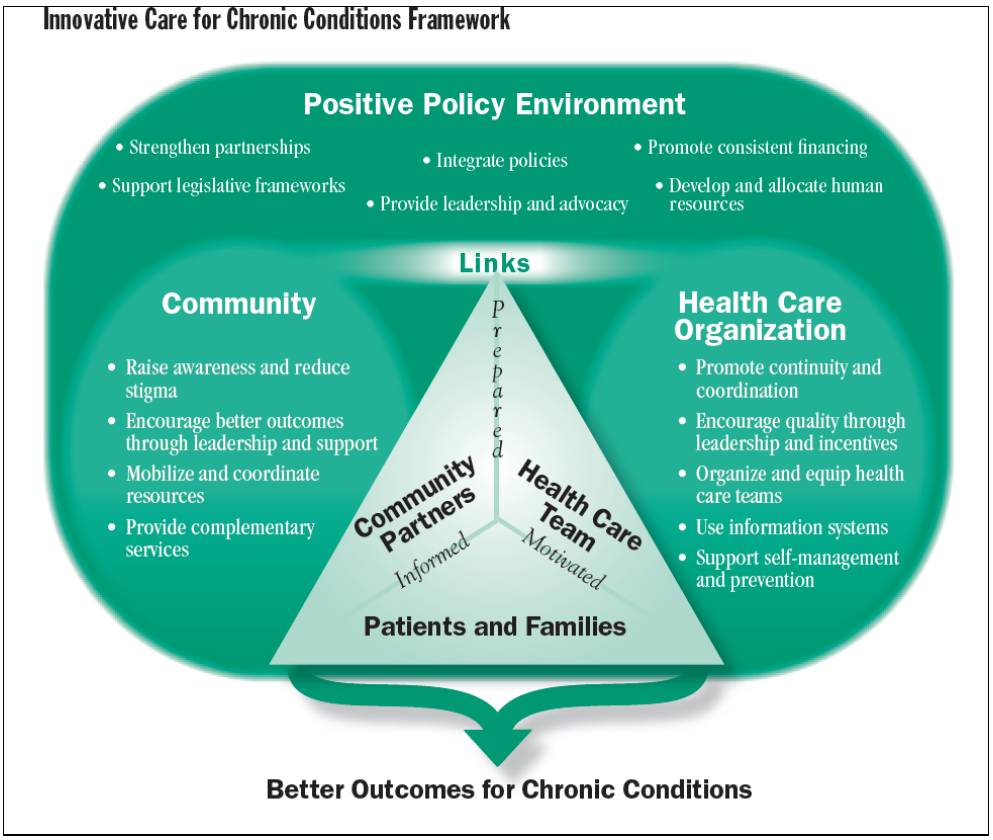
The Policy notice[m] by the Department of Health of the UK "Supporting people with long term conditions: An NHS and social care model to support local innovation and integration", published in 2005, aims to provide a framework for the treatment of long term conditions. It draws on the 'chronic care model' researched and applied by Wagner and colleagues in Seattle, USA.

7.2.1.2 *The ICCC framework*

The Innovative Care for Chronic Conditions framework or ICCC framework (Figure 3) was developed by the WHO in 2002 starting from the CCM or Chronic Care Model.[180,181] It expands community and policy aspects of improving health care for chronic conditions and includes components at the micro (patient and family), meso (health care organisation and community), and macro (policy) levels.

[m] http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4100252

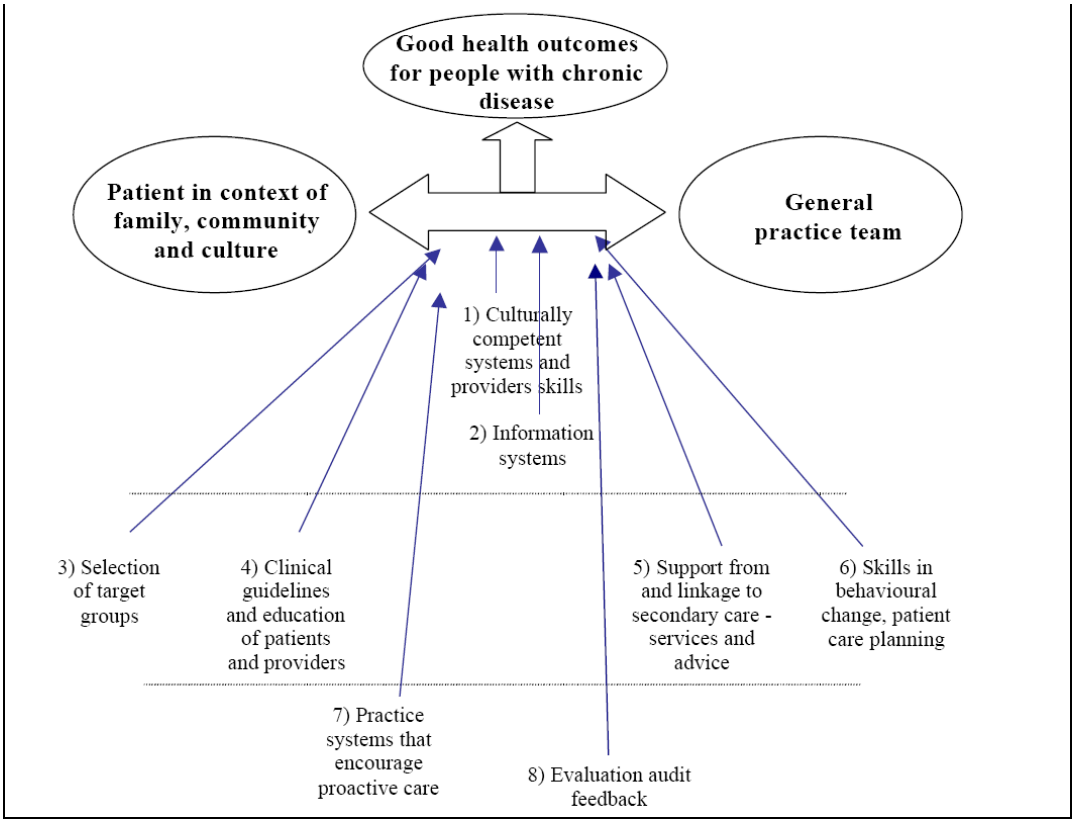
Figure 3. The ICCC or Innovative Care for Chronic Conditions Framework (WHO, 2002)



7.2.1.3 The New Zealand Chronic Care Management Programme

The third model has been developed in 2003 by Wellingham,[169] specifically to fit the problems encountered with chronic conditions in New Zealand; it has been called the New Zealand Chronic Care Management Programme (Figure 4).

Figure 4. The New Zealand Chronic Care Management Programme[169]



These three models share many elements in common, like emphasis on multidisciplinary care and comprehensive care strongly involving community services, integrated care and care coordination, the promotion of health-education and self-care, and a plea for the use of evidence-based guidelines and the use of information technology. This is not surprising, especially not for the ICCC which has been developed starting from the Chronic Care model.[180]

7.2.1.4 Disease Management Programs in chronic conditions

The fourth model, the Disease Management Programs (DMP), has been introduced in the early nineties, especially in the USA, and not primarily for chronic conditions. It is a means to coordinate care, focusing on the whole clinical course of a disease. Care is organised and delivered according to scientific evidence and patients are actively involved in order to achieve better health outcomes.[182] Although no single definition for DMP exists, its key elements are presented in Figure 5.

Figure 5. Disease Management Programs: Key elements.[182]

Disease Management: Key elements
- comprehensive care: multiprofessional, multidisciplinary, acute care, prevention and health promotion
- integrated care, care continuum, coordination of the different components
- population orientation (defined by a specific condition)
- active client-patient management tools (health education, empowerment, self-care)
- evidence-based guidelines, protocols, care pathways
- information technology, system solutions
- continuous quality improvement

Evidence on effectiveness of Disease Management Programs (DMPs) in improving care for people with chronic conditions[182] has been reviewed by the WHO (HEN-report 2003).

Again, the same elements included in the 3 models for chronic care management are found to be key components of the DMPs. It is concluded that DMPs, although differently implemented in different settings, improve the management for some chronic conditions (diabetes, depression, cardiovascular diseases) as measured by performance indicators e.g. adherence to guidelines. However, no evidence exists yet that specific DMPs improve the survival rate or quality of life. A systematic review by Ofman et al.[183] in 2004, in which experimental studies from 11 chronic conditions were included, came to the same conclusion, adding that no reduction in cost could be demonstrated. An important remark was that "results" of a DMP, when compared to "usual care" likely depend on the underlying health care system.

7.2.1.5 A Model of care for Chronic Fatigue Syndrome: conclusion

So far, no specific model of care for Chronic Fatigue Syndrome has been described in the literature.

Three models of care for Chronic Conditions were found, sharing many elements in common, like emphasis on multidisciplinary care and comprehensive care strongly involving community services, integrated care and care coordination, the promotion of health-education and self-care, and a plea for the use of evidence-based guidelines and the use of information technology. This is not surprising, since the second and third model were developed taking the first model into account.

The fourth model, the Disease Management Program (DMP), although primarily not developed for chronic conditions, emphasizes the same core elements as the three models for chronic care.

From the three models for Chronic Care that were found, the CCM has been mainly used to describe, introduce or study changes in the care of chronic conditions, and in several countries. Its components will be used to guide the comparison of the different CFS care modalities used in the selected Western countries.

7.2.2 Systematic review of management strategies for CFS patients in secondary versus primary care

During the search for evidence on the organisation of care for CFS, one systematic review was found discussing first level and second level care for CFS, irritable bowel syndrome and chronic back pain, and was retained for separate discussion.[184]

One more RCT on CBT in primary care for CFS patients was retrieved,[91] but in this trial group CBT was evaluated, so direct comparison with trials in which individual therapy had been provided is difficult. Another RCT evaluated CBT by general practitioners in a group of employees with unexplained fatigue, of whom 44% met the CDC-criteria of CFS at inclusion.[185] However, the CBT in this RCT was of much lower intensity (5 to 7 sessions of 30 min each) as compared to the CBT offered in the secondary-care studies mentioned in the review of Raine et al.[184]

In the review of Raine et al.[184] 3 randomised controlled studies (RCTs) on GET in secondary care were included, but no RCT in primary care. Four respectively one RCT(s) on CBT in secondary respectively primary care were included. It was concluded that CBT seems to be effective in secondary care patients (short term follow-up), and one study suggested that results of CBT and counselling in primary care might be equivocal (however, only 6 sessions of CBT or counselling were provided, as opposed to the 13-16 hours of CBT offered in the secondary-care studies). No definitive conclusions on effectiveness in secondary versus primary care can be made.

7.3 DEVELOPMENT OF A QUESTIONNAIRE AND SELECTION OF COUNTRIES

As described in the previous paragraph, the Chronic Care Model (CCM) had been selected to guide the comparison of the different CFS care modalities used in the selected Western countries.

However, the Chronic Care Model defines general organisational principles, rather than specific rules on how to describe comprehensively care organisation in a certain country.

Therefore, in agreement with the Process Notes on Health Services Research used by the KCE, the template for health system analysis published by the European Observatory on Health Systems and Policies[186] was used to develop the basis for the questionnaire that would be used to look for information on the selected Western countries. Elements of the Chronic Care Model not clearly represented in this general document, were added. Before it was finally adopted for use, the questionnaire was discussed with 2 other KCE researchers and with the president of the CSF/ME Working Group of the Belgian Superior Health Council (Benjamin Fischler, MD, PhD). The final questionnaire is presented in the Appendix 2A.

Following questions were addressed:

- Is incidence or prevalence of CFS known in other countries?
- How are CFS patients taken care of? Are there any specific structures or services available for CFS patients?
- If so, which professionals take care of CFS patients? Which diagnostic procedures and/or therapeutic programs are provided? Is scientific evidence taken into account? Is outcome registered or studied?
- Who is paying for these structures/services? What is the role of public funding? Patient out-of-pocket payments?
- What are therapeutic possibilities if no specific services are provided?
- How well does the provided care fit the elements of the Chronic Care Model?
- How are children or adolescents with CFS looked after?
- How are severely affected patients looked after?
- Are there special initiatives promoting return to work?

For the selection of countries, it was decided to discuss Western developed countries that were at least interested in care for CSF/ME. Countries for which already scientific work or other documents on CFS had been found, as an indication of some interest going on in the field, were selected. Contact persons of these countries, known to the experts participating in this study, were asked for their contribution in the project. Next, a list of scientists willing to contribute to a future European project on CFS[n] was consulted. After this process, persons from the UK, the Netherlands, Italy, Norway and Australia were found willing to cooperate. They were sent the questionnaire (for a list of contact persons, see Appendix 2B). Because only very few documents including official data were found, the numbers mentioned in this part of the study are expert estimations unless otherwise mentioned, and should be viewed with caution.

7.4 UNITED KINGDOM: ENGLAND

7.4.1 The CFS Service Investment Programme: Summary

The CFS Service Investment Programme, started up in 2004 in England by the NHS, and evaluated in 2006, has been the main source of the description given in this report. It is completed using information from experts in England, as listed in the Appendix 2B. Other UK regions are not (yet) covered by the CFS Service Investment Programme.

The total NHS funding for 2004-2006 amounted to 8.5 million English Pounds (£) (about 10.8 million Euros). This NHS funding has now been taken over by local trusts and/or private initiatives, in line with the general structure of the British health care system. Few CFS teams report that local Trusts are not willing to continue to fund services, which threatens further activities of the team.

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[n] list provided by one of the experts, Mrs Greta Moorkens, M.D., PhD, Head of the Department of Internal Medicine, University Hospitals Antwerp, Belgium.

The estimated prevalence of CFS in the UK is 0.2% of self-reported ME in the general population, and 0.6 to 2.6% among primary care patients.

7.4.1.1 General features: the CNCCs, LMDTs and Specialist Teams for children and young people.

General concepts for CFS services are:

- a levelled model of services, networking with local services and health care workers,
- aiming to provide patient centred care,
- including a comprehensive range of services for CFS patients and good accessibility,
- by trained professionals,
- part of formal and informal networks, and in contact with voluntary organizations.

Thirteen Clinical Network Co-ordinating Centres (CNCCs), 36 Local Multidisciplinary Teams for adults (LMDTs) and 11 specialist teams for Children and Young People have been established. They cover 65% of England; 84% of the UK population lives in England. This means that 32 million of the 50.7 million inhabitants of England are covered (Total inhabitants in the United Kingdom (2006)[o]: 60.5 million).

The CNCCs aim to support the development of multidisciplinary teams within a geographic area (including development of local teams, providing access to specialist advice (consultancy), provision of training by lectures, symposia, workshops; provision of a treatment manual[p] for professionals or direct supervision of professionals, etc.). They sometimes also act as a LMDT. A few CNCCs are involved in international peer-reviewed research.

The LMDTs' mission is to provide 1) access to assessment and diagnosis (some LMDTs do not provide a diagnostic service themselves as the diagnosis is expected to be made in primary care); 2) support for adjustment and coping and 3) symptom management and rehabilitation strategies.

The specialist teams for Children and Young People aim to establish a specialist expert resource for care of children and young persons suffering from CFS; some teams exclusively focus on adolescents. Services include support in diagnosis and management as well as training of local paediatricians or community health workers, and some direct provision of care. Additionally, many adult teams have a "link paediatrician" who facilitates care for children and young persons; and 23 adult teams have transition policies in place, for transition of young persons to adult services.

The services developed by the CNCCs/LMDTs are exclusively for CFS patients as no funded services previously existed for this patient group. Between 2004 and the end of 2006, 11 040 adults and 669 children suffering from CFS had been seen. Since strong decentralisation is a general feature of the British health care system, no fixed model of service has been imposed by the NHS. This implies that CNCC/LMDTs have been developed in accordance with local needs and opportunities, and that many service models are currently in use. Some teams cover large areas (e.g. 150 GP practices), others are smaller. Some teams provide only part-time services (e.g. 2 days/week). Networking with local services is a general feature of all CNCCs and LMDTs and a very important, essential part of the concept. Owing to the service variables e.g. decentralisation, development of services in accordance with local needs and opportunities, varying population sizes, different models of networking with local services, quantitative evaluation of the available services is very difficult. The following is a general summary of the information available.

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o http://www.statistics.gov.uk/CCI/nugget.asp?ID=6

p E.g. treatment manual of CFS Research and Treatment Unit of King's College, London, see Appendix 3. Books: "Overcoming chronic fatigue" (Burgess and Chalder), "Coping with chronic fatigue" (Chalder).

7.4.1.2 Team members

Lead of the multidisciplinary team can be a professional from any clinical background (physician, CFS nurse specialist, clinical psychologist, occupational therapists). Team composition is variable but teams may have physicians, psychiatrists, CFS nurse specialists, clinical psychologists, occupational therapists, cognitive behaviour therapists, physiotherapists.

Physicians involved in the team can be from varying background; about 50% are GPs or GPwSIs (GPs with Special Interest).

In many services, team members are available on a part time basis; in some teams services are only available on a part time basis (see examples in Appendix 3).

The team of King's College (London), consists of 3.2 FTE staff (see Appendix 3), some additional assessments are done by other specialists.

This team evaluates an average of 440 referrals per year and provides therapy for an average of 250 patients per year. The team of Kingston and Sutton /St Helier LMDT for CFS consists of 4 FTE staff and additionally 0.3 FTE consultant for about 560 new cases per year and an area of 1 473 000 million inhabitants.

7.4.1.3 Referral

Only CFS patients are accepted in CFS services. Waiting lists used to be common. However, as part of the government drive to bring waiting times down, the "18 week pathway" was introduced.

This means that the referral to treatment time should not exceed 18 weeks which means that patients need to have been assessed within 5 weeks.

Referral is through the patient's GP or through a medical specialist. In some CFS teams, medical diagnosis needs to be confirmed by the clinician of the team, in other teams it is mandatory that the diagnosis has been confirmed before referral. Most teams support local GPs during the process of diagnosis. Usually a network is available with local specialists to assess difficult cases (if no medical specialist is member of the team). Referral forms are often available requiring demographic data, medical history, prevalent diagnostic symptoms, date of start of symptoms, co-morbidities and results of investigations are required to be accepted into the CFS service. Investigations are mostly blood tests as specified in the NICE guidance

The referring GP and/or medical specialist should always receive a copy of the treatment plan, of re-evaluations, and of the discharge summary. Sometimes, the referring GP or specialist is also involved in the team discussion of initial treatment or discharge plan. Treatments that can be provided equally well by local non specialist services are preferred to treatments by the CFS LMDT.

7.4.1.4 Adult services

Many different service models and approaches have been developed so far, each CNCC and LMDT trying to respond to local needs and opportunities in the most efficient way.

REHABILITATION SERVICES

Some care pathways explicitly refer mild cases to their own GP for treatment. (e.g. St Helier Model of Care, for their definition of mild-moderate-severe, see Appendix 4).

In most LMDTs, the management plan discussed at the MDT meeting will be agreed with the patient. Often this discussion will take place between the assessing therapist and the patient unless the case is particularly complex and requires the input of other team members. The letter sent to the GP with the proposed management plan is also sent to the patient.

For mild, moderate or severe cases, group therapies are available as well as individual therapies on an outpatient basis, group therapy being more common in some teams. However, it should be noted that one of the most successful teams, the CFS Research and Treatment Unit of King's College (London), only provides individual therapy. Often, teams liaise with local therapists or services, which then provide therapy under guidance of the CFS team.

Most therapies are time-limited (e.g. 8 weeks for group therapy, 12 sessions fortnightly with a cognitive behavioural psychotherapist and 24 sessions fortnightly with a clinical psychologist). Usually follow-up is provided, e.g. at 3, 6 and 12 months after intervention.

Examples of therapy provided are GET, CBT, pacing, relaxation, stress management, energy management, sleep management, strategies for memory and concentration, managing set backs. No information has been found on which therapy model prevails most. The general impression is that most services providing CBT or GET use a model adapted to the specific needs of CFS persons. One centre, the CFS Research and Treatment Unit of King's College, London, exclusively offers CBT or GET. Their therapy manual[q] can be found in the Appendix 5.

The same centre is also participating in a multi-centre RCT on pacing. A Group program Manual from the Leeds and West-Yorkshire CFS service (9 weeks, 1 meeting/week) is available at www.CFSpod.net. However, unlike the manual of the King's College Team, this group manual has not proven yet its therapeutic value in a scientific trial, preferably a RCT.

Not much information has been found on projects set up specifically for occupational rehabilitation or employment issues, although these problems can be dealt with in the provided therapies (e.g. CBT, counselling…).

A national guideline is provided by NHS-Plus[r].

For the severely affected (home- or bedridden) persons, 27/36 LMDTs provide at least some intervention for this group. Domiciliary assessment is available in most of these 27 teams; some teams also provide rehabilitation, usually only during a limited time period and in collaboration with local therapists or community services. Recently initiatives have been taken to link these services with other NHS-initiatives for management of long-term conditions (MLTC), which also raised the question whether case management should be started. It should also be mentioned that eight national CFS inpatients beds are available (Essex Neuroscience Team); inpatient service is also possible in some other hospitals.

OTHER SERVICES

Telephone contacts, supportive e-mails or help-lines are often provided. The CFS Research and Treatment Unit of King's College, London, is conducting a RCT on telephone/postal CBT. In many LMDTs leaflets, books, self-care diaries, information on patient support groups or websites are available.

The NHS supports group programs that reinforce self-help in patients ("NHS Professional led Programme"). Many services provide patients with a group programme manual or session handouts, to reinforce course content.

The EPP or Expert Patient Programme (a generic lay-led group workshop) was introduced into the NHS in 2001. A trial for 34 CFS patients, yielded mixed feedback regarding the suitability of the program for CFS.

Many Self-help groups exist, based on initiatives of patients themselves who meet or "chat" to offer each other practical and emotional support.

7.4.1.5 Provided services for children and young persons

A number of Specialist Teams for children and young people have identified treatment possibilities within generic paediatric services, providing a central role for the local paediatrician. Other Specialist Teams provide direct care to the patients. Some teams have paediatric services utilising resources within the adult team. Links with local youth therapists are provided in some teams.

According to the available information, rehabilitation for children and young people can include CBT, pacing and/or GET. It is more often on an individual basis as compared to

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q A more extended version of the therapy manual can be found in two books: "Overcoming chronic fatigue" (Burgess, Chalder); "Coping with chronic fatigue" (Chalder)

r 'Occupational Aspects of the management of CFS: a National Guideline' www.nhsplus.nhs.uk

adults' rehabilitation. Also, domiciliary services seem to be more common than in CFS adults. However, age- and severity-specific groups for children exist, as well as parent-support groups. Attention is being paid to inform school and teachers.

7.4.1.6 Outcomes

Registration of a Minimal Data Set (MDS) started April, 2006; data are collected locally; the national process of central collection has not yet been finalized.

The data has to be collected when the patient is first seen by the service and again (only once) between 9 and 15 months after the first assessment. The following items are included: demographic information including employment or educational status, clinical information related to diagnosis, and validated outcome scales (on severity of symptoms (Chalder Fatigue Scale), mood (Hospital Anxiety and Depression Scale; HADS), pain severity (Visual Analogue Scale for Pain), physical function (SF36 Physical Function), perceived improvement (Clinical Global Improvement Scale).

One service, the CFS Research and Treatment Unit of King's College, London, published the results of 384 patients treated in their service.[102] It should be noted that another 135 patients of the same cohort (1995-2000) were not offered treatment at assessment, mainly because of primary diagnosis of major depression (70 persons) and not meeting diagnostic CFS criteria or refusing CBT (42 persons). Average age at entrance was 39 years (SD 11 yrs) and average duration of the fatigue was 5.3 years (SD 4.6 yrs).

After an average outpatient treatment duration of 11.3 hours (SD 4.8 hours), on an *individual* basis, patients improved on the Chalder Fatigue Scale[68] from 8.5 points to 6 points at 6 months follow-up (cut-off for extreme fatigue on this scale: 4 points). On the Work and Social Adjustment Scale,[187] patients improved from 5.5 to 4 points at 6 months follow-up.

7.4.1.7 Discharge from the CFS Service

Details of discharge policy were found for one LMDT (St Helier CFS Model of Service, see Appendix 4) and are briefly presented below.

BEFORE THE INTERVENTION IS COMPLETE

Following completion of the sessions patients will be discussed within the MDT meetings; often these discussions take place between the treating therapist and the patient and not necessarily the whole team and either followed-up by another member of the team where appropriate or discharged back to the care of the GP. A discharge report will be sent to both the referrer and the GP. Patients are usually sent a copy of their discharge report.

There are a number of scenarios in which a patient may be discharged before the intervention is complete. These would include:

- Unwillingness on the part of the patient to engage in a bio-psychosocial model of intervention.
- 2 consecutive DNAs ("Did Not Attend") following an initial assessment or cancellation of 3 appointments within the therapeutic contract.
- Little sign of change/progress even after a number of sessions.
- Abusive or aggressive behaviour.

AFTER THE INTERVENTION

CFS is a long term condition and it is recognised that people with CFS may need care and support over a long period of time. In order for the specialist CFS service to have sufficient capacity to deal with new referrals, a formal discharge process will ensure that people are formally assessed for discharge, given a contact number for further support and advice and if necessary referred on to other support agencies.

The decision to discharge the patient from the CFS service will be agreed at the MDT or between the patient and the therapist. The discharge criteria for patients with CFS are:

1. Improvement in the fatigue that allows return to work, school or previous levels activity.
2. Alternative diagnosis made on basis of clinical assessment and laboratory tests. Patient referred onwards for specialist management.
3. Stabilisation of the fatigue with level of functioning acceptable to the patient.
4. CFS still variable but patient provided with full range of physical and mental strategies to cope with the illness. Patient discharged with support by the CFS team and with the understanding that telephone advice can be provided.
5. Patient unable or chooses not to engage in treatments offered by the service

7.4.1.8 Payment

Reimbursement for the services of the CNCC/LMDT is claimed from the Primary Care Trust baseline budgets (or Mental Health Trusts); the patient does not pay at the point of service delivery. Information obtained from one service (the CFS Research and Treatment Unit of King's College, London) revealed that, in 2002-2003, of the 431 referrals, 37 were denied funding by the PCT and hence could not be seen. For 2003-2004, this concerned 37 patients out of 408 referrals (approximately 9% of patients.)

7.4.2 Services provided in regions in England not covered by the CFS Service Investment Programme

No information available from the contacted experts.

Key points

- **The estimated prevalence of CFS in the UK is 0.2% of self-reported CFS in the general population, and 0.6 to 2.6% among primary care patients.**
- **Levelled care for CFS has been started up in 2004 in England.**
- **An area of 32 million people is served by: 13 coordinating centres (CNCCs), 36 local multidisciplinary teams for adults, and 13 specialist teams for children and young people.**
- **Services are exclusively for CFS patients; within the first two years of the project, 11 040 adults and 669 children suffering from CFS had been seen.**
- **Networking with local services is an essential part of the concept.**
- **Also teaching, supervision and outreach of/to local services in the community are well-integrated concepts.**
- **Team composition and provided services differ according to local opportunities and needs, in agreement with the national British health care system.**
- **50% of the physicians involved in the teams are GPs or GPwSIs (GPs with special interest).**
- **Medical referral is necessary, standard referral forms are mostly available.**
- **Most teams only accept well-diagnosed patients; GPs are supported in the diagnostic process; for difficult diagnoses links to second or third level specialists are provided or diagnosis is made within the team.**
- **Treatment is mostly by the team, usually on an outpatient basis; treatment plans are discussed with the patient and the referring medical doctor. Sometimes treatment is provided by local services, supervised by the LMDT.**
- **Some teams refer mild cases to the patient's GP for treatment.**
- **Most therapies are time-limited (e.g. 8 weeks for group therapy, 12 sessions fortnightly with a cognitive behavioural psychotherapist and 24 sessions fortnightly with a clinical psychologist). Usually follow-up is provided, e.g. at 3, 6 and 12 months after intervention.**
- **Several therapies are provided, group therapies are common. One of the large centres (King's College London) exclusively provides CBT or GET, and pacing (in a multi-site RCT), on an individual basis. This centre also provides Therapy Manuals.**

- **Domiciliary services including time-limited therapy for severe cases are available in many teams. Local community services are involved as much as possible.**
- **Eight national CFS inpatient places are available for severe cases (Essex Neuroscience team).**
- **Other services, like telephone contacts, leaflets… are available. Information sessions for family members exist (but are not provided everywhere).**
- **For children and young people, individual and domiciliary services are frequently used. Contacts with local services are important.**
- **From April 2006 on, a minimal data set on outcome is registered by the centres; no outcome results are available yet.**
- **In the starting phase of the services (2004-2006), the Government exceptionally provided 10.8 million Euros to the centres. This has now been taken over by the general British health care reimbursement system.**

7.5 THE NETHERLANDS

So far, no specific structurally available care organization(s) for CFS has been set up in the Netherlands. Recently, the Dutch Government asked to develop guidelines on CFS, to increase research on effects of scientifically proven treatments for CFS when they are applied in daily life; and to increase the availability of CBT, an evidence-based treatment for CFS (see further). It is estimated that 30 000 to 40 000 CFS-patients live in the Netherlands[s], for a total of 16.4 million inhabitants (Centraal Bureau Statistiek, 2007). This means an estimated prevalence of 0.2%.

Due to specific interest in the field of CFS, two Dutch centres, the University medical centre Nijmegen and the CFS Centre Amsterdam, developed a specific service for CFS patients. However, direct accessibility of these services is limited to the Nijmegen and Amsterdam region, although they get referrals from a much broader area (see further).

The Nijmegen service[t], the "Nijmeegs Kenniscentrum Chronische Vermoeidheid" (NKCV) started its activities in the late eighties, and is now an internationally recognized centre for CFS. The NKCV acquired experience with CBT for CFS, which led to several high-quality publications. Also fatigue due to chronic disease (e.g. cancer) is treated in the centre.

An average CBT-treatment (protocol based) for CFS in the NKCV takes about six months and comprises 16 sessions, on an individual basis. Patients should be referred by their GP or by the medical specialist; online advice to GPs on the diagnosis is provided. If necessary, the diagnosis can be further explored in the NKCV. Only patients not involved in another therapy for fatigue are accepted for treatment. Likewise, if patients enter an appeal to the court, they are excluded from the therapy as long as this procedure lasts (so this exclusion criterion for acceptance is temporary). Patients can be refunded from their private health insurance, depending on the contract they have.

Due to persisting long waiting lists (more than 300 patients), the NKCV decided to start teaching behaviour therapists outside the NKCV. A trial has been started up in the Centre for Mental Health Care (GGZ) in Oost Gelderland, and recently also in the GGZ Westelijk Noord-Brabant. Teaching sessions are organized, and behaviour therapists can qualify after a 30 hour teaching program and supervision. On-line information for patients and health care workers on CFS is available on the NKCV website.

The "CFS Research centre Amsterdam", nowadays called the "CFS Centre Amsterdam" was funded[u] in 1998, by the Foundation for Metabolic Disorders. Three medical specialists have been developing fundamental aetiological research on CFS, including drug trials for CFS, leading to several publications in this field. A special point of interest

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s Health Council of the Netherlands. Chronic fatigue syndrome. The Hague: Health Council of the Netherlands, 2005; publication no. 2005/02. (http://www.gr.nl/)

t http://www.nkcv.org/; Nijmeegs Kenniscentrum Chronische Vermoeidheid (NKCV)

u http://www.cfscentrumamsterdam.nl/index.htm

is carnitine treatment; whereby the aim is to improve complaints or symptoms (not to cure the patient). The CFS Centre Amsterdam sees about 800 CFS patients a year. All evidence-based therapies are discussed with the patient, and provided according to the patient's preference (or the patient is referred to the centre that offers the therapy). No specific medical referral is necessary. In case of uncertainty, the diagnosis is confined/ rejected in the centre before the treatment is started. CFS and also fatigue in other chronic diseases (e.g. cancer) are treated in the centre. If patients are not fully covered by their health insurance for the treatment, they are let off the rest if they are not able to pay.

On-line information for patients and health care workers on CFS is available on the website of the Amsterdam centre.

The centre of Nijmegen and the Wilhelmina Children's hospital of Utrecht have a special service for children from 11 years and older. CBT is offered with involvement of the family.

No information was found on family information sessions by the NKCV or the Amsterdam centre, or organised by patient associations. However, the NKCV gives several presentations and workshops open to patients and patient organisations as well as to professionals (physicians, nurses, psychologists etc.)

In the Netherlands, the Government asked an advice on CFS from the Health Council ("Gezondheidsraad"), resulting in 2005 in a report clarifying the current state of knowledge on CFS[v]. One of the advices in this report was to ask the CBO, the Dutch Health Care Quality Improvement Institute [w] or "Kwaliteitsinstituut voor de gezondheidszorg" to develop guidelines for a more uniform approach to CFS-patients throughout the country. These guidelines will be available in the nearby future.

ZonMW, an organisation aiming at improving health, health care and prevention by stimulating and developing the transfer from basic knowledge to practical implementation[x], was asked to develop a program to increase the knowledge on/ stimulate the use of the to-develop-guidelines, and to increase the capacity for CBT-treatment, which actually at that time was only available in Nijmegen at the "Nijmeegs Kenniscentrum Chronische Vermoeidheid". ZonMW should also increase research on effectiveness (as opposed to efficacy) of therapies like CBT, GET and pacing for patients in day-to-day life. The ZonMW program has been started up and first results are awaited (+/- 2010).

In 2007, the Health Council published a protocol to inform and advice medical advisers of insurance companies on CFS[y].

Key points

- **The prevalence of CFS in the Netherlands is estimated at 0.2%.**
- **No specific structurally available CFS care services have been set up in the Netherlands.**
- **Two centres with specific interest and research in CFS (Nijmegen and Amsterdam) provide diagnostic and therapeutic possibilities.**
- **Also fatigue in other chronic disorders (e.g. cancer) is treated in these centres.**
- **One of the two centres only accepts patients on GP referral.**
- **Treatment is on an outpatient, individual basis. Group sessions are not available.**

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v Health Council of the Netherlands. Chronic fatigue syndrome. The Hague: Health Council of the Netherlands, 2005; publication no. 2005/02. http://www.gr.nl/

w http://www.cbo.nl/home_html

x http://www.zonmw.nl/nl/organisatie/ (Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie)

y Verzekeringsgeneeskundige protocollen. Chronische-vermoeidheidssyndroom. Lumbosacraal radiculair syndroom. Gezondheidsraad, 2007/12, april 2007; http://www.gr.nl/pdf.php?ID=1532&p=1

- **Evidence-based rehabilitation treatments for CFS, especially (time-limited) CBT, are available around the region of Nijmegen.**
- **Outreach to other regions and teaching of CBT are being developed under support of the Government.**
- **The centre of Nijmegen and the Wilhelmina Children's hospital of Utrecht have a special service for children (from 11 years on).**
- **No information was found on specific family information sessions on CFS.**
- **Reimbursement of centres and acts is according to the national health insurance system, without specific conditions or restraints for CFS.**
- **The Amsterdam centre lets off fees if the patient can't pay.**
- **The government supports the development of Dutch guidelines, which will be available in the nearby future; a protocol on CFS for medical advisers of insurance companies exists.**

7.6 ITALY

In Italy, no prevalence numbers for CFS are available.

Four centres in Italy provide specific services to CFS, fibromyalgia and CFS-like syndromes (e.g. cancer-related fatigue): the University hospitals of Chieti and of Pisa (third-line), the hospital of Aviano (second-line), and a charity-based service in Pavia. These centres provide diagnosis, time-limited treatment, and follow-up. Three other second-line hospitals provide diagnostic possibilities: Rome, Verona and Bari. All activities are on an outpatient basis, except in Chieti where admission is possible. This centre has also set up clinical research. It is estimated that each centre on average treats/ sees 100 patients per year, of which about 50 new patients. Since Italy has about 57 million inhabitants, this means that about one patient is seen per 100 000 inhabitants. Waiting lists do not exist. The services are run by medical specialists (rheumatology, neurology, infectious diseases, and oncology); in the four specialized centres psychiatrists and/or psychologists also belong to the multidisciplinary team. Contact with first-line (or second line) services is by phone or (medical) letter, as usual among physicians.

Diagnosis by one of these services is necessary to be recognized as CFS-patient. Referral by a medical doctor is not necessary. Educational sessions for patients or family, and support (leaflets…) for self-care, are available. Treatment in the four specialized centres is time-limited (e.g. 3-4 months in Pavia) and on individual basis (no group sessions). General psychotherapy is provided, but CBT is not; nor is GET or pacing. Physiotherapy if indicated is provided in private practices outside the centres. Sometimes alternative therapies (acupuncture, homeopathy) are provided. Occupational rehabilitation, telephone support, assessment at home for severely affected cases or specific programs for self-care are not provided. Patient outcomes are not routinely evaluated. Psychotherapy can also be followed outside the centres, and is reimbursed in Italy.

No services for children exist. Assessment or treatment at home for severe cases is not available; nor is outreach and/or teaching to support local rehabilitation teams, health workers or social workers.

Reimbursement of the centres is by regional or local health authorities; one of them (Pavia) is funded by charity. Acts are reimbursed according to the national health insurance system, without specific conditions or restraints for CFS.

Key points

- **No prevalence of CFS in Italy is known.**
- **Three general centres provide diagnostic possibilities; four specific centres also provide time-limited treatment and follow-up. No specific services for children exist.**
- **Number of CFS-patients seen: about 1 / 100 000 Italian inhabitants (based on expert opinion).**
- **Diagnosis by one of these centres is necessary to be recognised as CFS-patient.**
- **Treatment is on outpatient, individual basis; one centre also admits patients. Group sessions are not available.**
- **Family and patient information sessions on CFS are available; as well as time-limited psychotherapy.**
- **Evidence-based treatments for CFS, like CBT and GET, are not yet available.**
- **Contacts with primary care are as usual among physicians; centres do not provide outreach to bedridden patients or support/ teaching to local health or social workers.**
- **Reimbursement of centres and acts is according to the national health insurance system, without specific conditions or restraints for CFS. One centre (Pavia) is funded by charity.**
- **No Italian guidelines are available.**

7.7 NORWAY

No specific Norwegian prevalence numbers for CFS are available.

Norway has 3 University hospitals (third-line) where CFS patients are seen, as part from routine neurology/ infectious diseases/ paediatric practices: 2 for adults (Oslo and Bergen) and one for children (Rikshospitalet, Oslo).

7.7.1 CSF/ME care for adults

The adult centres provide diagnosis, coping classes, and some limited individual therapy. Activities are usually on an outpatient basis. For the CFS service of Oslo in the Ullevaal University Hospital, covering approximately half of the Norwegian population, it is estimated that on average 350-400 patients per year are seen/ treated, of which about 300 new patients. Of the new referrals, approximately 2/3 gets the diagnosis of CFS. The adult service in Bergen (Haukeland University Hospital) grew mainly after a generalised Giardia infection of the main water supply some years ago, infecting many people. Afterwards, a peak in CFS prevalence was noticed. Since Norway has about 4.7 million inhabitants, it can be estimated very roughly based on the Oslo numbers that yearly about 16 adult patients for 100 000 inhabitants are seen in these two adult centres. However, diagnosis can be set by other medical specialists as well. Diagnosis is mandatory to be recognized as a CFS patient.

Apart from the two University centres, most large hospitals throughout the country provide general rehabilitation programs for all sorts of diagnoses. Included are "Coping centres", specific services for chronic disorders of different kinds. CFS patients can also get services in these Coping centres.

Information for this study on the current working of the adult University CFS services (e.g. numbers used in the next paragraphs), could be obtained from the Oslo Ullevaal University Hospital.

So far, patients need a referral from a medical doctor to be seen in the University hospital. The waiting list is about 9-12 months. Coping course/classes for patients are provided (8 times 2 hours; maximum 15 patients); the patients are allowed to bring one relative or care taker on the day the doctor talks about what CFS is. Information meetings (3 hours) are also arranged twice a year, where relatives and care takers can

come. The coping course/class is based on teaching patients pacing techniques and energy economizing (occupational therapist), deep relaxation (physiotherapist), knowledge about the disease (doctor), conversation with psychiatric nurse about reactions to being ill and coping, information about healthy food for patients with CFS (nutritional expert) and information on how to obtain social security money for people who have been away from work more than one year and how they can get financial support for technical aids. In the near future, classes based on CBT and GET techniques will be started up, as part of a research project. Individual therapies (general psychotherapy, physiotherapy, pacing, occupational rehabilitation, self-care programs and eventually alternative therapies (homeopathy…) are possible, but usually classes are provided. All these therapies, including CBT and GET but excluding pacing are also available for CFS (and other patients) outside the University centres, but only scarcely. Educational sessions on CFS are also available outside the centres.

For severe cases, assessment and treatment can be delivered at home by the University hospitals; limited telephone support is also available.

Apart from the national service for children in Rikshospitalet (see further), the Oslo Ullevaal University Hospital also provides a coping class for children and parents.

Reimbursement is given for the whole period of the classes (8 weeks), and for the medical consultations/acts in the hospital. Individual therapy in the hospital is reimbursed if patients get the service as part of the coping classes. Otherwise it has to be financed by the hospital's regular budget, except for psychotherapy which is not reimbursed. Reimbursement is not time-limited. Reimbursement for therapy outside the University hospitals is provided under the general health care system, without specific conditions or restraints for CFS patients compared to other diseases. Educational sessions on CFS are not reimbursed.

7.7.2 CFS care for children and adolescents

The interest for CFS in children and adolescents at the University Hospital of Oslo (Rikshospitalet), started almost six years ago, and initially was purely scientific. However, soon thereafter, other children's hospitals in the country started to refer their patients, and clinical services were started up. Nowadays, all other Norwegian children's hospitals belong to the Rikshospitalet's network. In 2007, approximately 80 patients were seen. The team nowadays consists of 2 paediatricians (involved for 20% respectively 40% FTE), a nurse (50% FTE); as well as an occupational therapist, physiotherapist and dietician (each for 30% FTE available). A child psychiatrist can be consulted in Rikshospitalet if necessary, but it is required that the child has been seen by a child psychiatrist in the local hospital before referral. Given the absence of definite scientific criteria for CFS in children, the team agreed on the following criteria to make the diagnosis of CFS: the child has been fatigued for at least 3 months (but usually fatigue already exists for at least 6 to 7months), without other conditions causing the fatigue; the fatigue should be "severe", i.e. it should have caused absence from school for a considerable time period. Children suffering from fatigue due to a medical condition e.g. cancer treatment, are seen as well, but rather exceptionally. After referral, patients stay 2 days in the hospital for a multidisciplinary evaluation. The parents are not charged for this service (don't pay anything). At the end of these two days, the results are discussed extensively with the parents and if possible with the child. A treatment planning is proposed, and contact persons in the child's neighbourhood are proposed that can be contacted to provide the therapy (on an individual basis). Usually an adapted form of GET is provided, in which gradual increase of a broad range of activities is proposed, according to the age, possibilities and the interest of the child. CBT can be proposed as well, but is less readily available. At home, the planning agreed on is taken over by the local paediatrician or community service. The child is seen every 2 or 3 weeks and activities increased if possible. So far, no systematic follow-up in the Rikshospitalet is provided, but this will be established in the nearby future.

7.7.3 New initiatives as from 2007

In 2007, a report has been published on the care of CFS in Norway. Since clear information (e.g. numbers of patients) on organisation of care was scarce, and since apparently some Norwegian regions had almost no services in place for this group of

patients, the Minister decided to provide extra money to several new initiatives. The main focus is twofold: 1. to inform the public but also primary and secondary care and social services on CFS and CFS care; 2. to develop or improve care for and/or knowledge on care for this patient group "in the field". The Health Directorate (an independent national service providing support in policy making) has been authorized to guide the implementation of these initiatives, called the "National Competence Network for CFS". A yearly budget of 5 million Norwegian Kröne during 3 years (2007-2008-2009), or 15 million Kröne (approximately 1.9 million Euro) have been made available.

As part of the care improvement, the Oslo Ullevaal University Hospital has been asked to provide a special CSF/ME interdisciplinary outpatient clinic and ambulatory team for adults for a region covering approximately half of the Norwegian population. Rikshospitalet is asked to provide a similar service for children. This is worked out as a project and starts in august 2008. For the adults, the team will be led by a full-time GP; 1.5 FTE medical specialists (neurology, psychiatry and internal medicine), 1.5 FTE psychiatric nurse/social worker and 1.5 FTE therapists (occupational therapy, physiotherapy) will be member of the team. Outreach or visit to support local rehabilitation teams, health and social workers is already available now, but will be expanded and made more structurally available in the project (e.g. if necessary one of the team members will attend a meeting in the community where the patient lives to start a care plan).

Another initiative consists in a better implementation of GET.

Apart from the yearly budget, an extra budget of 3.2 million Kröne (approximately 405.000 Euro) has been made available to the University Hospital in Bergen, for the specific problems related to the infectious episode in the past.

A new initiative for the most severe cases consists in the development of a national inpatient service of 10 beds, for which additional money will be provided.

A systematic literature review on CFS diagnosis and treatment has been published by the "Nasjonalt kunnskapssenter for helsetjenesten".

Key points

- **No prevalence of CFS in Norway is known.**
- **Two University hospitals provide diagnostic possibilities, coping classes and some limited individual therapy for adults. One University hospital provides specific services for children.**
- **Referral by a medical doctor is required; there are waiting lists of 9-12 months.**
- **Number of adult CFS patients seen yearly: 16 / 100 000 Norwegian inhabitants (based on expert opinion).**
- **Number of CFS children seen yearly: 80 (for 4.7 million inhabitants).**
- **Diagnosis by one of the centres, or by another medical specialist, is necessary to be recognised as CFS patient.**
- **Coping classes comprising 8 sessions and maximal 15 patients are the main treatment option for adults; individual therapy is available but very limited. Pacing and relaxation are included.**
- **Evidence-based treatments for CFS, like CBT and GET, are planned in the near future (in the classes).**
- **Family members can attend the coping classes.**
- **Service at home for bedridden patients is possible; therapy for children is on an individual basis and in the local community.**
- **Reimbursement of services in the University hospitals favours (for adults) the coping classes over individual therapy; reimbursement outside these services is provided under the general health care system, without specific conditions or restraints for CFS patients.**

- **In 2007, the Minister decided to provide extra funds during 3 years to improve information on and care-in-the-field for this patient group, under the guidance of the Health Directorate.**
- **Outreach or visit to support local rehabilitation teams, health and social workers is limited available now, but will be expanded in this project that will start in the Oslo region (adults- children) in August 2008.**
- **A systematic literature review on diagnosis and management has been published in Norwegian.**

7.8 AUSTRALIA

The point all over prevalence of CFS in Australia is estimated on 0.2-0.5%. The Government finances guidelines (e.g. GP guidelines, that were sent to all GPs in South Australia in 2004), but no special services for CFS exist (yet).

However, care for CFS patients is possible in non-exclusive services (i.e. services open to all sorts of diseases).

Psychotherapy for CFS patients is readily available, and reimbursed like for other diseases, which means that many patients pay for it themselves. However, therapists providing CBT (cognitive behaviour therapy) are rather scarce.

Physiotherapy is available and reimbursed, but only very few therapists provide GET (graded exercise therapy) and GET is not reimbursed. As far as known, pacing is not available.

Occupational therapy is only available and reimbursed under certain circumstances, like for other diseases.

Educational sessions on CFS for patients and family are sometimes available (not reimbursed); programs promoting self-care are rather scarce, and also not reimbursed.

For children, only few paediatric hospitals also take care of CFS patients, as part of their general services.

Severely affected CFS patients not able to work or to support themselves are provided for by the Government Disability Support Pension Scheme; some patients also access Income Protection Insurance or the superannuation funds before retirement. Little support is available for adults in need of personal assistance in daily life that who do not have relatives to look after them. These persons are looked after via the public hospital system.

Key points

- **The point all over prevalence of CFS in Australia is estimated on 0.2-0.5%.**
- **The Australian Government supports the development of CFS guidelines for GPs, but no special structures for these patients are available.**
- **Family and patient information sessions on CFS are available (no reimbursement).**
- **Evidence-based treatments for CFS, like CBT and GET, are scarce. CBT is reimbursed (like in other disorders) but GET is not.**
- **A few paediatric hospitals take care of children with CFS.**

7.9 COMPARISON OF CFS CARE IN THE DIFFERENT COUNTRIES AND CONCLUSION

A general overview of CFS care for adults in the countries described, as compared to Belgium, is given in Table 13.

Table 13. Comparison of CFS care for adults in selected countries

ADULTS	United Kingdom: England	The Netherlands	Italy	Norway	Australia	Belgium
Specific settings CSF/ME	Yes: 13 coordinating centres or CNCCs; 36 local multidisciplinary teams or LMDTs (covering 32.5 million people; i.e. 65% of 50 million inhabitants of England)	Yes: 2 university hospitals (16.4 million inhabitants)	Yes: 4 centres diagnosis and therapy, 3 centres diagnosis (57 million inhabitants)	Yes: 2 university hospitals (4.7 million inhabitants)	No	Yes: 4 reference centres (10.5 million inhabitants)
Level of specific settings	Third and second level (coordinating centres and local multidisciplinary teams); networking with local hospitals and community care to provide care locally when possible/ appropriate	Third level; networking with secondary level centres (Centres for Mental Health Care or GGZ) to provide care locally when possible/ appropriate	Third and second level	Third level. Under development in one centre (Project, start 8/2008): networking with local hospitals and community care to provide care locally when possible/ appropriate	N.A.	Third level; networking with community care planned but not developed yet
Settings recognized by Government	Yes (since 2004)	No (however, networking with secondary level is supported by Government)	No information	Yes (since 2007)	N.A.	Yes (since 2002)
Other diagnoses than CFS included	No	Yes: fatigue related to severe medical conditions (e.g. cancer)	Yes: fatigue related to severe medical conditions (e.g. cancer); fibromyalgia	No	N.A.	No
Referral by medical doctor necessary	Yes	Yes for one centre	No	Yes	N.A.	Yes
Yearly diagnostic plus therapeutic capacity of all settings/100 000 inhabitants	17/100 000 (numbers based on Government report)	No information	1/100 000 (50% new patients) (numbers based on expert estimation only)	16/100 000 (75% new patients; 66% confirmed CFS diagnosis (numbers based on expert estimation only)	N.A.	5/100 000; 96% confirmed CFS diagnosis (numbers based on Government report)
Waiting lists	Yes; but Government	Yes	No	Yes (9-12 months)	N.A.	Yes (in 3 of 4 centres)

ADULTS	United Kingdom: England	The Netherlands	Italy	Norway	Australia	Belgium
	imposes "18 week pathway": assessment within 5 weeks, referral to treatment time should not exceed 18 weeks					
Diagnosis	Online support of referring M.D. to make diagnosis, blood samples as in NICE guideline. Special referral forms. If necessary further explored by CFS centre or referral to medical specialist of network when no M.D. part of the CFS team.	Online support of referring M.D. to make diagnosis, if necessary further explored by CFS centre. Special referral form.	By the CFS centre	By medical specialist (belonging or not to the CFS centre)	N.A.	Special referral form. Diagnosis confirmed or if necessary further explored by CFS centre
Predominant treatment content (other than medication if needed)	Several options; recently general evolution toward CBT (some centres exclusively CBT, GET or (in trial) pacing)	One centre specific medical treatments. Other centre CBT, it does not accept patients as long as involved in other therapy for fatigue or gone to court	General psychotherapy	Coping classes with several components; recently beginning evolution toward GET (or CBT), in coping classes	N.A.	CBT and GET together
Treatment manual (CBT or GET) in one or more centres available	Yes (CBT), efficacy approved in research applications	Yes (CBT), efficacy approved in research applications	No	No	N.A.	Manual in each centre; efficacy not approved in research applications
Usual treatment (based on expert information only, except Belgium): individually or group / in- or outpatient	Group sessions most used, but individual therapy possible; some large centres exclusively individual therapy / outpatient usually but 8 national CFS beds and	Individual treatment only/ mostly outpatient	Individual treatment only/ mostly outpatient but one centre specialized inpatient service	Group sessions (coping classes) most used; individual therapy rarely/ mostly outpatient but one centre with specialized inpatient service to start in nearby	N.A.	Group sessions in 83% of time and individual therapy in 17% of time; outpatient mostly; inpatient possible but rarely (based on Government report)

ADULTS	United Kingdom: England	The Netherlands	Italy	Norway	Australia	Belgium
	inpatient possible in general hospitals. Note: one centre refers mild patients to own GP for treatment			future (separate Project; funds will be foreseen for start-up)		
Treatment period: average duration per patient	Many different approaches (see Appendix); usually time-limited e.g. 8 sessions for group therapy, 12 to 24 sessions individually fortnightly with psychologist	CBT: 16 sessions of 60 min. spread over 6 months	3 to 4 months psychological therapy (expert opinion only)	Coping classes: 2 hours 1x/week during 8 weeks	N.A.	Total 41 to 62 hours spread over 6 to 12 months
Treatment provider	Multidisciplinary team. Lead of the team can be professional from any clinical background. Physicians involved in the team for 50% GP or GPwSI (GP with special interest)	Multidisciplinary team (one centre)	Lead of the team medical specialist; psychologist or psychiatrist for psychological therapy	Multidisciplinary team; lead of the outreach team (Project to start 8/2008) will be GP	N.A.	Multidisciplinary team; lead of the team medical specialist
Personnel available	According to local needs and opportunities; some teams offer only part-time services; team members usually only part-time. One team (King's College London) of 3.2 FTE staff (some additional assessment by other staff not included) 443 referrals in 1 year; 177 patients CFS not confirmed (40%); 246 patients treatment	No information	No information	One centre starts Project (8/2008) implementing outreach and teaching to area of 2.3 million inhabitants by team of 1 FTE GP; 1.5 FTE medical specialists; 1.5 FTE therapists; 1.5 FTE nurse and social worker (total 5.5 FTE).	N.A.	18.25 FTE for 4 centres together (+/-550 evaluations and 407 treatments yearly) (numbers based on Government report)

ADULTS	United Kingdom: England	The Netherlands	Italy	Norway	Australia	Belgium
	(55%); other examples see Appendix.					
Outreach, teaching	Yes, strong focus especially for coordinating centres	Yes: one centre: teaching of secondary level centres (Centra Geestelijke Gezondheid)	No	To start in 8/2008 (Project)	N.A.	Option made available by Government but implemented very limited so far
Family information sessions	Available in several teams	No information	Yes	Yes	N.A. (available through patient associations)	Yes
Provision of on-line information, leaflets…	Yes	Yes	Yes	Yes	N.A. (available through patient associations)	Yes
Provision of specific self help programs	Some limited experience	No information	No information	No information	No information	No
Occupational rehabilitation, support to regain work	Subject dealt with if necessary, but no specific program	Subject dealt with if necessary, but no specific program	No specific program	Subject dealt with if necessary, but no specific program	N.A.	Subject dealt with if necessary, but no specific program
Assessment or limited treatment at home for severely affected	Possible in most LMDTs	No information	Not possible	Not possible	N.A.	Not possible
Provision for severely affected not able to work	Disability funds, like in other patient groups; NHS-protocol available for medical advisers of insurance company	Disability funds, like in other patient groups; protocol by Health Council available for medical advisers of insurance company	Disability funds, like in other patient groups	Disability funds, like in other patient groups	Disability funds, like in other patient groups	Disability funds, like in other patient groups
Outcome registration	Systematically in all centres; uniform list of outcome scales	If patient included in study protocol; parameters registered dependent on study concept, different in 2 centres	No	To start up in nearby future	N.A.	Systematically in all centres; uniform list of outcome scales

ADULTS	United Kingdom: England	The Netherlands	Italy	Norway	Australia	Belgium
Reimbursement	NHS special funds from 2004-2006; afterwards been taken over by national health insurance system as for other disorders but some Primary Care Trusts refuse reimbursement for CFS	National health insurance system as for other disorders; one centre takes personal situation into account	National health insurance system as for other disorders	National health insurance system as for other disorders including separate funding for coping classes; additional special funds for Project starting 2007 for at least 3 years.	N.A.	Special RIZIV/INAMI funds from 2002-2008
Therapy outside CFS settings, not specifically devoted to CFS: content (expert opinion only)	No information	No information	General psychotherapy or physiotherapy, CBT or GET extremely rare	Psychotherapy or physiotherapy; rarely CBT or GET	Psycho-therapy or physiotherapy CBT, GET or pacing very rare	Physiotherapy available but GET is rare. Psychotherapy available but specific CBT for CFS rare.
Therapy outside CFS settings, not specifically devoted to CFS: reimbursement	No information	No information	Psychotherapy or physiotherapy reimbursed (like in other disorders)	Psychotherapy, CBT or physiotherapy (or GET by physiotherapist) reimbursed (like in other disorders)	Psychotherapy, CBT or physiotherapy reimbursed (like in other disorders); GET or pacing not reimbursed	Physiotherapy or GET by physiotherapist reimbursed at special rate (like some other selected disorders); psychotherapy or CBT only reimbursed in Centres for Mental Health Care (CGGZ/Services de Santé Mentale) (like in other disorders)
National guidelines, supported by the Government	Yes, by NICE	Underway (CBO)	No	No	Yes (in South Australia sent to all GPs)	Yes, by Superior Health Council

N.A.: not applicable

7.9.1 Organisation

Two separate tendencies are found in the organization of CFS care in The United Kingdom, Australia, The Netherlands, Italy and Norway.

1. No specific and structurally available care for CFS is organized, but the Government stimulates the development of guidelines, protocols…

This is the case in Australia, and in a certain way also in The Netherlands. In the Netherlands, two CFS centres exist (and a children's hospital involved in care for CFS children) that were initiated 10 to 20 years ago as a result of specific scientific interest of these institutes. Both centres also offer therapy to CFS-like syndromes (e.g. cancer-related fatigue); there is a multidisciplinary approach. Access is limited to the own region, but outreach and teaching to other professionals has been set up in Nijmegen, and is supported by the government.

2. Specific and structurally available care for CFS patients is organized by the Government, mostly recently i.e. a few years ago. This is the case for Italy, Norway and the UK (England). Networking and integration of these services with care in the community vary in the 3 countries.

In Italy, the centres are run by medical specialists, working together with psychiatrists and psychologists. The care for CFS patients is also offered to CFS-like syndromes (e.g. cancer-related fatigue) and fibromyalgia. Access is very limited; networking with community health care workers is also very limited. One centre is funded by charity.

In Norway, two multidisciplinary university services for adults offer therapeutic group sessions for CFS patients. No other diagnoses are accepted. Due to long waiting-lists, access is limited. From August 2008 on, the Government funds a project in which several local teams in the community will be set up under supervision of one of the University adult services. One university service offers specific advice for children.

In 2004, the NHS provided extra funds to England, to set up special structures exclusively for CFS patients. A large part of England (65%) has been covered since then, and waiting lists already exist. The provided services are structured in separate levels: 13 CNCCs or coordinating centres, 36 LMDTs or local multidisciplinary teams for adults, and networking with health and social care workers in the community. Eleven specialist teams for children coordinate the care for children, in collaboration with adult teams, local hospitals or community health care workers. The LMDTs are explicitly multidisciplinary. Physicians involved in the team are GPs in 50% of the cases. In accordance with the vision of decentralisation in the British health care system, no fixed model of care has been imposed by the NHS.

7.9.2 Adult Therapy

The therapy provided can be group based and/or individual.

In The Netherlands and Italy, the therapy is exclusively individual. Evidence-based strategies (and especially CBT) are very common in the Netherlands and spread over +/-16 sessions (6 months). In Italy, CBT and GET are not yet used; therapy takes on average a few months.

In Norway, the largest part of the adult therapy are group sessions (8 sessions, 2 months), individual therapy is possible but not common (due to financial restraints of the hospital). CBT and GET will be set up in a research protocol in the nearby future.

In The UK, both group therapy and individual therapy are possible, and depend on the local options and possibilities. Therapies are time-limited (e.g. 8 group sessions; one year of fortnightly individual psychotherapy sessions). Group sessions are most frequently used, but one of the most successful and internationally well-known teams, the team of King's College, London, provides mainly individual sessions. CBT and/or GET are used by some centres, but not by others.

In no centre, a specific approach to professional support for those patients in need of it could be traced; however, occupational issues if necessary are part of the general therapeutic strategy (e.g. CBT, counselling…).

7.9.3 Services for children and young people

In the UK, the Netherlands and Norway specific services are available for children and young people. Not enough information is available on the different components of these services, to compare the countries on this point.

7.9.4 IT support

IT support, according to the Chronic Care model a component necessary to facilitate the care for chronic patients (by supporting coordinated patient appointments etc.) is available in all evaluated countries.

7.9.5 Family information sessions

Family information sessions are available in most countries; also in Australia where it is provided by the patient organisations. In The Netherlands, no information on family information sessions could be found, but information or teaching sessions open to family members and/or professionals are provided by one centre.

7.9.6 Websites, patient information for self-help

In all countries, websites for patients, patient information leaflets etc. are available. Patient information is an important component of the Chronic Care Model.

7.9.7 Outcome registration

In The Netherlands, outcomes are systematically registered during trials. The UK is the only country that developed and implemented a patient outcome registration system that is used by nearly all LMDTs. Several validated outcome scales are included. However, it is still too early to conclude from the data gathered by the system.

7.9.8 Conclusion

Recently, specific services for care of CFS patients have been set up in several, but not all of the evaluated countries. Care organisation of these services and therapy provided vary from one country to another. They fit to a varying degree the Chronic Care Model.

The UK system is the most developed one. It is organised in separate levels, implying central coordinating centres on the one hand, local multidisciplinary teams in the middle, and a strong networking with local services on the other hand. Although a patient outcome registration system has been implemented, no results are available yet. Also for the other countries, no evaluation of the provided care organisation has been undertaken yet.

The absence of outcome results limits the possibility to decide which organisational model is to prefer.

More research is necessary in the field of CFS, especially on the implications of different forms of care organisation.

Key points

- **Two separate tendencies are found in the organisation of CFS care in the investigated countries.**
- **In the England, Norway and Italy, specific and structurally available care for CFS patients is organised by the Government.**
- **On the contrary, in Australia and the Netherlands no specific and structurally available care is organised by the Government. However, the development of guidelines and protocols is stimulated.**
- **In England and Norway, and in the University-based centres in the Netherlands, the care is provided in a multidisciplinary way.**

- **In England and the Netherlands, GPs are stimulated to make the diagnosis, although in more difficult cases the CFS centre has to confirm it. In Italy, the CFS centres have a specific role in diagnosing CFS, whereas in Norway secondary care and the CFS centres are in charge of making diagnoses.**
- **No evidence exists on differences in diagnostic accuracy according to the care level where the diagnosis has been made.**
- **Most CFS centres use diagnostic protocols.**
- **In the United Kingdom, group therapy as well as individual therapy is provided, and usually group therapy is more prominent except for some large centres where individual therapy is most prevailing.**
- **In Norway, group therapy is mostly provided, whereas in the Netherlands and Italy only individual therapy is available.**
- **Therapy in the CFS centres is always time-limited, and therapy duration in Belgian CFS centres (between 42-61 hours/patient) seems to be longer than in other countries.**
- **In some countries, evidence-based therapies are provided (but nowhere systematically like in Belgium), in other countries not.**
- **In England and the Netherlands, therapy manuals validated by (randomized) clinical trials are available.**
- **The Chronic Care Model or CCM insists on care integration and comprehensive care involving community services. Adherence to this Model is variable; so far England fits it best.**
- **In England, CFS care is organised in separate levels, implying central coordinating centres, local multidiciplinary teams and strong networking with local services.**
- **The CCM also insists on promotion of health education and IT support in care organisation; both these items are available in all investigated countries. Family information sessions are also available in most countries. Experience in CFS with self-care, which is also a component of the CCM, is still limited (see England).**
- **In no country, specific programs aiming at return to work are provided, but professional issues are usually addressed in the other therapies.**
- **Experience with CFS children and young people exists in England, the Netherlands and Norway. It is usually still under development. Care provision seems to be mostly individual (England) and integrated in the child's natural environment (Norway).**
- **In England, care provision for severely affected persons in the home environment is usually available, but further development is going on.**
- **In England, a uniform outcome registration system is used by the CFS centres, but outcome results are not yet available.**
- **No data are yet available that inform on outcome of the different care models in the different countries. This limits the possibility to decide which organisational model is to prefer.**

8 DISCUSSION

8.1 BELGIAN CFS REFERENCE CENTRES FOR ADULTS

8.1.1 CFS Definition

In the scientific literature, several definitions of CFS[z] exist, of which no one has proven its added value on the others. The two most widely used definitions of CFS are the International Centre for Disease Control (CDC) 1994 definition (this replaced the original CDC 1988 version) and the British (Oxford) definition. The CDC 1994 definition is based on an international consensus of researchers and simplified the original 1988 definition by reducing the number of symptoms required and necessitating the exclusion of only a small number of specified psychiatric syndromes. In the Belgian Reference Centres (RCs), the 1994 CDC-criteria are currently in use.

All definitions include 6 months of invalidating fatigue as an essential criterion for the diagnosis of CFS. However, many clinicians consider that the six-month time period is an "end point" by which stage the diagnosis of CFS should have been confirmed, rather than, the point at which it should first be considered.

Although there is no evidence base, many treating practitioners in the field of CFS believe that patients would benefit from earlier referral for treatment, for example at the three month stage, rather than waiting until symptoms have been present for six months. Answering to this expectation, the NICE guidelines (2007) propose to make the diagnosis already after 4 months of unexplained fatigue. This advice has been formulated by the Guideline Development Group, without being endorsed by scientific evidence. Therefore, it should be validated scientifically before being introduced as the new standard criterion to diagnose CFS patients.

In the same way, NICE recommended a shorter duration of symptoms (3 months) to diagnose CFS in children and adolescents, arguing that 6 months of symptoms is too long for young persons. This argument has never been tested and seems to be particularly troublesome since the syndrome in adolescents usually resolves spontaneously and a premature diagnosis can lead to a "learned illness" state.

Because no unifying aetiological concept or definitive patho-physiological process leading to CFS has been described in the literature, the *biopsychosocial* model seems to offer patients and therapists the most coherent approach to understanding the problem and starting a treatment. This model suggests that once an illness has started its expression, it is affected by coping styles and behaviours, while consequential physiological and psychological effects act in some ways to maintain or modify the disease process.[9] The combination of each of these components is different for each patient. More research in the different fields of this model, biological as well as psychosocial, is necessary to fully understand the problem of CFS and to open the way to new treatment possibilities.

8.1.2 Severity

A severity grading was proposed by the NICE Guideline Development Group distinguishing mild, moderate and severe CFS patients.

Mild CFS –Individuals are mobile, can care for themselves and can do light domestic tasks with difficulty. The majority will still be working. However, in order to remain in work they will probably have stopped all leisure and social pursuits, often taking days off. Most will use the weekend to cope with the rest of the week.

Moderate CFS –Individuals have reduced mobility and are restricted in all activities of daily living, often having peaks and troughs of ability, dependent on the degree of symptoms. They have usually stopped work and require rest periods, often sleeping in

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[z] In this report, the term "Chronic Fatigue Syndrome" is used according to scientific definitions, which make a clear distinction between CFS and Fibromyalgia. However, in Belgium the terms CFS and Fibromyalgia are sometimes used interchangeably in daily language, which is not the case in this report.

the afternoon for one or two hours. Sleep quality at night is generally poor and disturbed.

Severe / Very Severe CFS - Will be able to carry out minimal daily tasks only (e.g. face washing, cleaning teeth) or are unable to mobilise and do any of these for themselves. Have severe cognitive difficulties and be wheelchair dependent for mobility. These people are often unable to leave the house except on rare occasions with severe prolonged after-effect from effort. They may also be in bed for the majority of the time and are often unable to tolerate any noise, and are generally extremely sensitive to light.

This classification, based on a consensus between NICE experts, was not tested in empirical researches. It could be difficult to be operational, both for researchers and clinicians. Using validated instruments and operational scales (MFI general fatigue, MOS SF-36 and Symptom Inventory Case Definition Subscale), Reeves et al.[26] grade CFS patients according to specific cut-offs on each of these scales.

8.1.3 Diagnosis

8.1.3.1 Diagnostic tests

Without "red flag" signs pointing towards other disorders, the diagnosis of CFS can only be established on symptoms and by excluding other medical conditions owing to routine blood analysis and routine urine analysis, including some and excluding other tests (see chapter 2.3.). The Belgian Guidelines proposed by the Superior Health Council, can be updated in line with this current literature evidence. This means that neither routine use of cortisoluria, serological tests, and L-RNAse are neither recommended nor routine evaluation of RX thorax, ECG or abdominal ultrasonography. Before other evaluations are routinely offered in addition to the examinations proposed by NICE, more scientific studies first have to confirm their impact on diagnosis as well as consecutive care for this group of patients. This is certainly true for polysomnography, that, although promising, points to the same number of primary sleep abnormalities in healthy controls and patients with CFS-like complaints. The result of treating these primary sleep abnormalities (also existing in healthy controls) on the CFS-like complaints still remains to be studied.

8.1.3.2 Role of primary care in the diagnostic process

The influence of the medical level-of-care (primary i.e. general practitioners, secondary i.e. medical specialists or general hospitals; or tertiary i.e. specific to CFS/ME) in accuracy and efficacy of diagnosing CFS/ME has not been studied scientifically so far.

According to the NICE guidelines, the diagnosis can be made by general practitioners. In Belgium, this seems to fit with the fact that, in +/-90% of patients referred to the RCs, the diagnosis of CFS suspected by the GP or another non-specialized service, could be confirmed.[167] In some other CFS centres for which numbers are available (e.g. King's College, London), a much higher percentage of the referrals is reoriented because the presumed diagnosis of CFS could not be confirmed. The reason for the difference between the Belgian RCs and these centres abroad is not clear; differences in referral pattern or diagnostic concepts are possible explanations.

NICE guidelines support that the initial investigations in individuals presenting with fatigue are likely to be undertaken by their general practitioner, with referral on to secondary care at a later stage, if appropriate. Uncertainty about another serious condition instead of CFS should be discussed with a medical specialist. Moreover, all severe cases should be referred to a specialist for CFS advice immediately. In mild and moderate cases, general management and treatment can be started up by the GP. However, referral to special CFS services should be discussed with mildly attained persons within 6 months of presentation, and with moderately attained persons within 3-4 months of presentation. Even after referral, the treatment should remain "integrated"; and, in mutual agreement with the patient, one professional should be the care coordinator.

The influence of the medical level-of-care (primary i.e. general practitioners, secondary i.e. medical specialists or general hospitals; or tertiary i.e. specific to CFS) in accuracy and efficacy of diagnosing CFS has not been studied scientifically so far.

It is striking to note that in the Belgian RCs, the amount of expenses devoted to diagnostic evaluations increases more than for rehabilitation. Focusing the RC activities on diagnostic evaluations is not in line with the NICE recommendations.

8.1.4 Treatment of CFS

Spontaneous recovery is most common within the first 5 years of illness. The proportion of CFS patients who fully recover without specific intervention (natural course) is low (median rate of 7%) while the proportion of CFS patients who improve is higher (median rate of 39.5%); the proportion increasing over time (after 5 and 10 years). However, the worsening of symptoms during follow-up occurs in 5-20% of CFS patients. The recovery is heavily impacted by the type of onset of the syndrome; acute onset due to infections for example frequently resolves spontaneously.

Prognosis for CFS children and teenagers is more encouraging, with partial or total recovery obtained after 3-4 years.

Although some CFS patients recover with or without treatment,[95] no therapy exists yet that can guarantee cure in all patients. Improvement, however, is possible in many persons although in some patients relapses and set-backs occur.[11, 95]

Because there is some evidence to indicate that the sooner a patient is treated, the better chance of return to a normal way of living,[11] an important point emphasized by NICE is that symptom management should not be delayed until a definitive diagnosis is established.

According to NICE, all healthcare professionals should aim to establish a supportive and collaborative relationship with the CFS person and her/his family or carers. Shared decision-making between the person with CFS and the professional should take place during all phases of care. Treatment and care should be patient-centred and take into account patients' individual needs and preferences.

The same aspects are emphasized in the Chronic Care Model. Some weak evidence found in other chronic conditions stresses that introducing (parts of) this concept can increase outcome for patients (see chapter 7).

Introducing these aspects in the care for CFS patients, might be a first step in dealing with their complaints not being taken seriously by many professionals (see chapter 5).

8.1.4.1 Pharmacological treatments

Current evidence shows no known pharmacological treatment or cure for CFS. Symptom management should be as in usual clinical practice. For recommendations, see chapter 2.5.

No details on effects of drug treatment have been given in the Belgian reference centres' evaluation report (2006).[167]

8.1.4.2 Rehabilitation

WHICH THERAPIES TO USE?

At this moment, no one treatment has been shown to provide a "cure" for all cases of CFS. The only treatment strategies, for which clear evidence for benefit exists, are CBT and GET. Although pacing, based on the principle of balancing activity and rest, is favoured by some patients, there is no published trial evidence of its efficacy. A large multi-centre RCT, PACE is currently under way in the UK, comparing standardised specialist medical care with CBT, GET and pacing. Its results are not expected until 2009.

CBT includes planned activity and rest, graded increases in activity, establishing a sleep routine and cognitive restructuring of unhelpful beliefs and assumptions, in collaboration with the patient. GET involves a structured activity management programme that aims

for a gradual increase in aerobic activities, usually walking. Patients negotiate an exercise programme adapted to their own physical capacity. Patients are advised not to exceed the negotiated exercise duration or intensity.

According to the literature, CBT is effective on physical functioning, psychological well-being, quality of life and general health (work and social adjustment, long term goals). However, it is not effective for all patients. GET is effective on fatigue, health-related quality of life and perceived functional capacity although there is no evidence (yet) that GET improves real activity levels. So far, it has not been proven that GET does improve anxiety or depression. On the other hand, there is no evidence that GET may worsen outcomes. Like CBT, GET is not effective for all patients. However, higher drop-out rates for GET were observed in one large study than for CBT.

A strength of the Belgian RCs is the routinely use of evidence-based therapies.

However, several aspects of care delivery in the Belgian RCs deserve further evaluation in well-designed studies since evidence for effectiveness of these aspects so far remains limited (See chapter 2.5).

Effectiveness of CBT in *group therapy* has only been studied in one good quality level RCT and in a lower quality non-randomised waiting list controlled study, suggesting that group's therapy was effective; however, it was less effective than individual therapy. No study addressed properly the problem of the *number of therapy sessions* necessary for improvement. The Belgian RCs use on average 41 to 62 hours of therapy per patient, which is more than described in clinical trials in the literature (in many trials 10-16 hours).[18] Another point is that in the Belgian RCs, a combination of *CBT and GET* is provided. The added value of the combination of these therapeutic strategies has not been investigated yet.

Taking into account the routinely use of evidence-based therapies in the Belgian RCs, the outcome results obtained (based on the systematic outcome registration of all four RCs) can be considered disappointing. The reason for this is not obvious; many different factors might have interfered to confound the results.

Striking is also the difference between the 3 Dutch speaking centres, and the French speaking centre. Whereas the Dutch speaking centres quickly reached their provided capacity, the French speaking centre still reached only 50% of its capacity in 2005 (the last year included in the RIZIV/INAMI report). The reason for this is also not clear.

THERAPY CONTENT AND THERAPIST'S TRAINING IN CFS

It is generally agreed on in the literature, that CBT and GET provided to CFS patients should be adapted to this specific condition. This is also acknowledged by NICE. In their guidelines, general advice is given on therapy content, as well as on aspects of these therapies that can be offered when access to CBT or GET is not available. In the literature, several examples of therapy manuals are available, that have proven their value in scientific studies on this subject (see chapter 2.5.5 and chapter 6).

In the Belgian RCs, each centre uses a specific therapy manual including CBT and GET. It would be interesting to compare Belgian manuals and schemes approved in scientific studies, in order to assess common features as well as differences.

In research trials, CBT and GET have largely been delivered by experienced therapists. According to these trials, there is less potential for favourable outcomes if the therapy is delivered by less qualified/ experienced therapists (see chapter 2.5.3). This is also acknowledged by NICE. It is not clear according to which protocol professionals providing daily therapy in the Belgian RCs are trained.

According to the lack of evidence about effectiveness of individual v group therapy, and about combination of GET and CBT v separate therapy, an ongoing reassessment of treatment modalities and accessibility to specialized care should be recommended.

COST-EFFECTIVENESS OF CBT

Although CBT and GET have proven to be effective in CFS, only one prospective RCT reports on cost-effectiveness for CBT as compared to no treatment.[142] It appeared that

over a 14 months follow-up, the gain obtained by CBT over no treatment in quality of life (expressed as QALYs or quality adjusted life years), was only small and statistically uncertain, with a probability of 64% of increase in quality of life after CBT therapy. It should be noted that outcomes of this study correspond well with the outcome evaluation of the Belgian RCs, where conflicting results on quality of life after treatment were found.

Further, from a payers' perspective (health insurers and patients), CBT is found to significantly increase the total direct medical costs. However, it should be noted that direct medical costs other than the cost of the CBT (e.g. cost for additional medical examinations), as well as direct non-medical costs (e.g. costs of travelling to seek care) were lower for the CBT group as compared to the no-treatment group.

CBT became cost saving (context of the Netherlands) when not only direct medical and non-medical costs, but also indirect costs were taken into account, i.e. when a societal perspective is adopted. Under this perspective, the days that patients were unable to work because of their condition were valued and incorporated in the calculations; and it appeared that the additional costs for CBT were largely compensated for by the reduction in loss of productivity of the treated patients. However, this conclusion remains uncertain, since the estimated probability that CBT reduces total costs over "no treatment" is only 54%. More studies are necessary before a clear conclusion on the cost-effectiveness of CBT is possible.

In this context, it is worthwhile to mention a study by Annemans et al. (2008), describing the economic consequences related to a delayed diagnosis in fibromyalgia syndrome, a similar though scientifically different group of patients.[146] Medical resource use and corresponding costs (in a British context) were calculated 10 years before and over 4 years after the diagnosis of fibromyalgia syndrome had been made. Making the diagnosis led to cost savings and a decrease in resource use: diagnostic tests, drug use, referrals as well as GP visits. Although it still remains to be proven, timely diagnosing CFS might decrease subsequent costs (due to medical shopping, extensive diagnostic tests, ineffective treatments …) as well.

SELF-CARE IN CFS

The Chronic Care Model emphasizes the role of self-care in chronic conditions. First results in England of a trial using a NHS-endorsed self-care program (the EPP or Expert Patient Programme) yielded mixed feed-back regarding suitability of the program for CFS. At least one registered trial in this field is underway, and more evidence is necessary to understand the possible role of self-care in CFS.

BACK TO WORK

Patients who had been ill for many years and experienced long periods of sickness absence have more difficulties to return to work.

One systematic review conducted by NHS-Plus Evidence based guidelines (2006)[16] did not identify any primary research on the best way to manage return to work in individuals with CFS. However, some advices were formulated to employers and CFS persons willing to restart work (see chapter 2.6). Additionally, the Dutch Health Council also proposed specific advices concerning return to work. No information could be retrieved in the international comparative study on projects promoting return to work for CFS persons.

FAMILY EDUCATION SESSIONS

No high-quality studies evaluated the effect of family education sessions, but according to the biopsychosocial model, and in agreement with the Chronic Care Model, it might be one of the elements contributing to the general impact of patient care for CFS.

All Belgian CFS centres started family sessions as part of their general therapy supply.

8.1.5 Integrated care delivery

According to the Chronic Care Model, as well as to the NICE guidelines for CFS, care should be delivered in an integrated and coordinated way between the different levels

of care. This was also an explicit task defined by the Belgian Government and the RIZIV/INAMI when the Reference Centres were established in 2002. Specific financing modalities for consults between first level care (GP) and the RCs were made available.

So far, this goal has not yet been attained by the RCs. On the other hand, little high-quality evidence is available on the effectiveness of care delivery to CFS patients in first or non-specialized second level. In an international context, this model has been implemented in England, where coordinating centres (CNCCs) and/or local multidisciplinary teams (LMDTs) discuss treatment plans with local care providers and provide outreach and teaching where necessary. Outcomes are registered in a uniform and systematic way, but no results are available yet. In many LMDTs, medical support is provided by GPwSIs (GPs with special interest). One LMDT systematically refers all its mildly attained patients to her/his GP. Since no evidence on effectiveness of this model is available yet, introducing a comparable model of care in Belgium should be done cautiously, and under monitoring of outcome results.

In a special situation are the severely affected persons, not able to attend specialist clinics. A trial that is currently under way is the "Fatigue intervention by nurses' evaluation (FINE trial). Treatments will be delivered in patients' homes, so this trial is particularly suited to those who are too ill to attend specialist clinics. FINE will compare usual medical care with supportive listening delivered by a trained nurse and pragmatic rehabilitation. In England, many LMDTs provide yet some kind of domiciliary service for this group of patients. In Belgium, this is not the case yet.

8.2 BELGIAN CFS REFERENCE CENTRE FOR CHILDREN

Evidence for children and adolescents is still limited; also the Belgian Reference centre (RC) for children so far only has a limited experience with this group.

According to NICE, the diagnosis should be based on the CDC criteria and made after 3 months of inexplicable fatigue. After 6 weeks of fatigue, referral to a paediatrician is advisable. Generally speaking, the prognosis is better in young people compared to adults. It has been demonstrated that CBT can improve adolescents, but more research is necessary. In the information found for the selected countries, therapy for children is provided usually individually.

The Belgian RC works in an integrated way, and offers advice and support in the child's home environment. Their experience is still limited. Adolescents have also been taken care for in a residential way in the "Zeepreventorium" (De Haan, Flanders). More research before definitively advising on care for CFS children and adolescents is necessary.

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Wettelijk depot : D/2008/10.273/58

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
33. Effecten en kosten van de vaccinatie van Belgische kinderen met geconjugeerd pneumokokkenvaccin. D/2006/10.273/21.
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