Author’s response to reviews

Title: European Consensus Statement on Diagnosis and Treatment of Adult ADHD

Authors:

Sandra j.j Kooij (s.kooij@psyq.nl)
Susanne Bejerot (susanne.bejerot@sll.se)
Andrew Blackwell (Andrew.Blackwell@camcog.com)
Herve Caci (caci.h@chu-nice.fr)
Mique Casas Brugué (micas@vhebron.net)
Pieter Jan Carpentier (picarpentier@planet.nl)
Dan Edvinsson (dan.edvinsson@akademiska.se)
John Fayyad (jfayyad@idraac.org)
Karin Foeken (k.foeken@wanadoo.fr)
Michael Fitzgerald (fitzi@iol.ie)
Veronique Gaillac (v.gaillac@ch-sainte-anne.fr)
Ylva Ginsberg (ylva.ginsberg@sll.se)
Chantal Henry (chantal.henry@bordeaux.inserm.fr)
Johanna Krause (drikrause@yahoo.com)
Michael B Lensing (michaelb.lensing@ullevaal.no)
Iris Manor (dan100@013net.net)
Helmut Niederhofer (helmutniederhofer@yahoo.de)
Carlos Nunes Filipe (cnfilipe@netcabo.pt)
Martin D Ohlmeier (ohlmeier.martin@mh-hannover.de)
Pierre Oswald (pierre.oswald@chpche ne.be)
Stefano Pallanti (s.pallanti@agora.it)
Artemios Pehlivanidis (apechlib@eginitio.uoa.gr)
Josep Antoni Ramos-Quiroga (jaramos@vhebron.net)
Maria Råstam (maria.rastam@pediat.gu.se)
Doris Ryffel-Rawak (doryffel@bluewin.ch)
Steven Stes (steven.stes@uc-kortenberg.be)
Philip J Asherson (philip.asherson@kcl.ac.uk)

Version: 2 Date: 19 July 2010

Author’s response to reviews: see over
Thank you to the editors and the reviewers for the very helpful comments and support for this paper. We have addressed the specific points made as follows and believe that this has further improved the paper. We have submitted two copies of the paper. The first with all track changes; and the second with the track changes removed.

**Reviewer 1's comments**

Q: The European Network Adult ADHD aims to increase awareness of ADHD and improve knowledge and patient care for adults with ADHD across Europe. This reviewer agrees with the main conclusion of the Consensus Statement concludes that despite ADHD being a prevalent and impairing lifelong condition in adults, it is currently under diagnosed and undertreated in many European countries with its attendant detrimental consequences to patients, families and society.

A: We thank the reviewer for these positive comments

Q: This reviewer also believes that this statement largely applies to pediatric ADHD as well. Although better recognized than adult ADHD, beyond a few notable exceptions like The Netherlands and Germany, there is little evidence that pediatric ADHD is a well recognized and treated in most European countries.

A: The reviewer may be correct, but the European Network Adult ADHD did not review the current situation for children, which is in most cases is better than for adults. However we do recognise the importance of this comment. Because of the focus on adults we have not made any additional changes in relation to this point.

Q: It is not clear the order of treatment proposed in the recommended algorithm. In addition, more clarity should be offered in matching the proposed treatments to the individual characteristics and needs of individual patients.

A: The second reviewer makes a similar point, so we have re-written this section to clarify our recommended algorithm. However there is currently little in the way of an evidence base for the order of treating comorbidities.

Q: The discussion of first and second line treatment is debatable. Second line treatment implies that it should be reserved only for patients who failed the fist line treatment which it is not the case for medicines approved for ADHD. It may be more appropriate to present the information as treaters first and second choice.

A: We will further clarify this information, because this did not mean to imply that drugs other than MPH could not be used as first-line treatments. However in Europe MPH is recommended at the first line treatment in most cases. MPH is recommended as first line because it has a greater average effect size than atomoxetine; and there are multiple IR and XR preparations available in Europe. Dexedrine or amphetamine based treatments are not given equal weight in Europe because currently the only available medication in most countries is IR Dexedrine, with no long acting option. However longer acting medications like Vyvanse are likely to be introduced soon and would make a good option. We now further clarify these points.

Level of interest An article of importance in its field
Quality of written English Acceptable
Statistical review No, the manuscript does not need to be seen by a statistician.
A: We agree with this reviewer that a statistician does not need to review this article because it contains no novel statistical analyses – we are therefore unsure why this was suggested by the second reviewer.

Declaration of competing interests I declare that I have no competing interests

**Reviewer 2's comments**

Major Revisions-
Q: 1st paragraph, last sentence: I'd make note that "partial remission" is a symptom count and that these patients still retain functional impairments, per Faraone paper, I believe.
A: We already clarify in the sentence before that partial remission refers to persistence of symptoms linked to significant functional impairments. We now further clarify the link to impairment in the following sentence as well.

Q: 2nd paragraph, last sentence: not sure I agree with this. A lot of inattentive subtype have persistent symptoms as the inattention sxs seem to persist with greater impact in adulthood than the hyperactivity/impulsivity
A: We agree and have therefore clarified the source of the information and provide a further sentence to clarify that other forms of ADHD also (commonly) persist into adult life.

Q: 4th paragraph, 1st sentence: Persistence rate should be reflected in a range as papers support 30% plus.
A: We were not sure which sentence the reviewer was referring to here, however we address the point raised in the following way: The true rate of persistence is difficult to determine because of the various different criteria and methods of applying diagnostic criteria in the literature. We therefore prefer to refer to the meta-analytic study of Faraone and colleagues which takes a systematic approach to the literature that was available at the time (Faraone et al., 2006). The main point of this paper established that around 2/3 of children with ADHD remain impaired from ADHD symptoms (whether syndromatic or symptomatic) at the age of 25 years. To help to clarify the issue raised by the reviewer, we have now added an additional section, later on in the paper, that clarifies the issues of persistence of impairments in adults whether they reach full diagnostic criteria based on symptom count or not.

Q: 5th paragraph: an additional reason for under diagnosis in Europe may be the ICD 10 criteria for both inattention and hyperactivity/impulsivity symptoms leaving no entity for inattentive subtype without H/I. This is in contrast to DSM-IV. If so, it might to helpful to mention.
A: We have considered this point but do not believe this is an issue – in fact nearly all psychiatrists and other mental health workers in Europe now use the broader DSM criteria.

Stigma in general-
Q: 2nd paragraph 11th line: as in "and psychiatric residencies" as there is very little if any teaching on adult ADHD in these residency programs.
A: We already include lack of education/training in this section. However to help clarify this further, we have expanded this section to clarify that training has been lacking at all levels of professional development.

Gene, environment...-
Q: 1st paragraph, line 9: This 30-40% may be a self-reporting bias in patients whose insight into symptoms is limited, and not an accurate rate of persistence. R. Barkley’s longututnal study shows that some ADHD adult don’t even recall being diagnosed with ADHD as a child. Should be noted.
A: The reasons for low heritability of self-rated ADHD symptoms in adult twin samples is complicated and cannot be easily summarized in a review article of this type. The bottom line is that the current evidence from large population twin datasets is clear - that self-rated ADHD symptoms are not very heritable. We now refer to two very large datasets with the same conclusions – one published and the other currently being prepared for submission. Furthermore, our recent analysis of a very large sample of 12-year old twins finds that self-ratings in adolescents are less heritable than parent informant data, but more heritable than self-rated ADHD in adults. There are also two published papers that find that retrospective self-report of ADHD symptoms in childhood by adults, is also more heritable than self-ratings of current ADHD symptoms. Overall the twin data suggest the following: parent ratings (~70-80%); teacher ratings (~70-80%); self-ratings in 12 year olds (~50%); retrospective childhood self ratings by adults (~50%); self ratings for current ADHD (~30-40%). The reasons are not too clear at this time, because these are not clinical samples, but rather these data are based on MZ/DZ correlations in general population samples – however this is the same approach that is used in nearly all twin studies of ADHD that give rise to the often cited heritability of 76%. The most likely explanation is that self-rated DSM-IV items in
adults are confounded in two main ways: 1) lack of awareness when self-rating ADHD symptoms; 2) confounded by adult onset disorders that also generate ADHD-like symptoms. There is however as yet no empirical data to resolve these questions, so we have to conclude that further work is needed to fully understand the extent of genetic influences on ADHD in adults.

Q: 1st paragraph, line 10 to end: This section is unclear. Are you trying to say that symptoms in first degree relatives are poor matched and therefore the genetic implication is questionable? Needs to be clearer.
A: That is correct – symptoms scores for ADHD in adult MZ pairs correlate around 30-35%, hence the low heritabilities. Our response also takes in the previous question on self-awareness of ADHD symptoms. Because not all of the data relating to twin studies using self-ratings and ADHD in adults is published; and the extrapolation from population twin studies to clinical cases is complicated to explain; and concepts such as ‘genetic’ correlations are not well understood by many clinicians; and this is not a paper on genetics of adult ADHD – we have decided in response to the reviewers comments to greatly simplify this section. We now summarise the risks to first degree relatives, briefly discuss heritability in population twin samples and provide conclusions on the likely reasons for low heritability in adult twin studies. The rest of this section is now deleted.

Q: 2nd paragraph, line 4: "remits" may be a function of symptom count threshold or functional level. Subthreshold symptoms doesn’t mean the disorder went away and much as it has changed with neurodevelopment and/or behavioral accommodation. These conceptual distinctions should be noted somewhere.
A: We have now expanded on this elsewhere in the manuscript (this section is about aetiological processes). In this section we wish to highlight that persistence/desistence of symptoms may have genetic influences, which current genetic study designs have the power to detect. Here we change the phrase from persistence/remission of the disorder, to persistence/remission of ADHD symptoms. (I assume that in reality persistence is in fact quantitative, so there is no simple threshold between persistence and remitted – however a sub-group will fall below impairing levels of ADHD symptoms)

Definition of ADHD-
Q: End of first paragraph: you may want to consider adding a short discussion of potential modifications in diagnostic criteria proposed for DSM-5 to be published 2013, same year for ICD-11. You can find this information at www.dsm5.org under childhood disorders.
A: Good idea – thanks for pointing out that we missed this. This is now added.

How to properly diagnosis ADHD-
Q: 2nd paragraph, line 9: this is currently the threshold proposed by DSM-5, however specificity needs to be assess in clinical settings as other acute psychiatric disorders would reach this symptoms count threshold
A: We now qualify this by pointing out the potential reduction of specificity to the ADHD diagnosis in using lower threshold symptom scores (for example when screening for ADHD). However this really only applies to cross-sectional data, because the diagnosis is also based on symptoms starting in childhood/adolescents and being persistent (trait-like) and impairing over time, and therefore not related to acute psychiatric disorders.

Q: Last paragraph: I would suggest adding a brief mention "that based on the high heritability, the likelihood that a parent has ADHD if the child has it, is 30%. If a child has ADHD, the likelihood that one of the parents has it is 50%. The presence of ADHD in a first degree relative increases the likelihood of ADHD's presence in the patient." or something like this. I find in clinical practice that this information adds weight to the accuracy of the diagnosis.
A: Thanks - We now mention that rates in first degree relatives is around 20% or higher (reported in various family studies with references) and that family history may help to clarify the nature of the disorder in some cases – however we do not wish to over emphasise this point because many people with ADHD do not have a first degree relative with a clear history of ADHD and this could lead to the diagnosis not being made, when it
Assessment process-
Q: 1st paragraph, last sentence: I'm unaware of any reliable soft neurologic signs seen in adults with pure ADHD. If so, this needs to be specifically referenced for adults with ADHD.
A: We agree on this point. We have changed this section to refer more generally to the child literature showing aetiological overlap with other neurodevelopmental problems (Dyslexia, autism spectrum, motor coordination) and that this might then also be expected in some adults with ADHD, but has yet to be systematically studied. So the point is changed to one of comorbid neurodevelopmental traits, rather than soft neurological signs.

Instruments for screening and diagnosis:
Q: 1st paragraph, line 5: I'd add the sensitivity and specificity on this scale to the manuscript.
A: We have now included this.

Q: 4th paragraph: I think this paragraph can be expanded to delineate the Biederman/Seidman research on EF in adult ADHD defined by neuropsychological testing vs Barkley's recent publication on the EF symptoms being more predictive of impairments.
A: The point we are making is that neuropsychology test data does not have sufficient predictive value to make the diagnosis of adult ADHD – this is important because some people think that if there is no cognitive deficit on cognitive performance tests then someone does not have ADHD – which it not the case. Further, we do not yet know which cognitive performance impairments represent mediating cognitive processes that lead directly to behavioural symptoms – because they may also represent pleiotropic effects of genes. Recent data shows little correlation/association between cognitive performance data and ecological EF behavioural data. Also there are several potentially valid cognitive models of ADHD. Overall this is a complex literature that we cannot review here. So we prefer to keep things simple by keeping to clinically useful information – that ecological EF deficits (rating scale measures) are good predictors of ADHD and its impairments, while cognitive performance (test) data lacks sufficient positive predictive value.

Action: We now add the recent Barkley reference relating to this question.

Treatment focus in comorbid ADHD-
Q: 1st paragraph, line 4: this position will be challenged by bipolar experts who will tell you a bipolar patient may be in a quiet phase of illness and that doesn't mean it gets discounted in the treatment algorithm.
A: Clearly if someone has recurrent episodes of mania/hypomania, they will need to be on mood stabilizers to control this. However if someone is in a 'quiet phase' of a bipolar disorder and has persistent impairing symptoms of ADHD from early childhood, they are likely to need treating for ADHD as well. We have altered to text to clarify this.

A: The "treat the most severe comorbidity first" is a carryover from child psychiatry. In addition, there is no good quality study that offers clinical guidance on this issue so clinicians have to make the best judgment to treat one condition without worsen another. It has been proposed to diagnostically prioritize comorbidity: first SUD/alcohol abuse, then severe mood disorders, then severe anxiety disorders, then ADHD. Milder depressive or anxious symptoms might be deferred until after treatment of ADHD. I think this section needs to be more instructive to adult clinicians.
A: We agree with your scheme as outlined and will amend this section for clarity. Since this is a consensus statement, we are providing the shared wisdom of the clinicians in the European group on this topic. The point is that serious comorbidities usually needs treating first – manic or depressive episodes, addiction disorder, and psychosis – but as you correctly point out treatment of mild depression and anxiety may be deferred to after the treatment of ADHD (and may then not need separate treatment). In some complex cases experience of treating ADHD is needed to formulate the best approaches for individual patients and such cases should be referred to specialists.
Q: 2nd paragraph, line 5: the collective work of Fran Levin in New York has not shown appreciable improvement in ADHD with it’s treatment in the presence of SUD. The severity of ADHD may play a role in deciding treatment but the patient needs the SUD treated as a primary disorder.
A: Agreed – we did not intend to indicate that SUD would not be treated as a primary disorder and will clarify this. We also now refer to some of the literature on treating ADHD in addiction/SUD patients. Treating ADHD can however be useful in some cases particularly where there is good understanding and compliance for the treatment program.

Pharmacotherapy for adult ADHD in Europe-
Q: 2nd paragraph, line 11: mention breastfeeding as well; clarify epilepsy as untreated epilepsy (recent review suggests stimulant have little effect on seizure threshold)
A: Okay - thanks

Q: 4th paragraph, line 4:delete "yet" as it seems like the next part distinguishes MPH from AMPH. I’d also suggest a sentence setting this up: The abuse potential according to N. Volkow's studies relates to the rate of serum rise. Therefore, agents injected or snorted which cause rapid elevations in dopamine levels are highly abusable." then go into your next sentence. In this way, you help the reader understand that abuse potential in based on route of adminstration and not the compound (MPH v AMPH)
A: We have further clarified this section

Q: 4th paragraph, last line: suggest text change "Therefore, medications, usually once daily dose, that have slow rate of serum rise are preferable in treatment to reduce potential for abuse and diversion." or something like this.
Types of stimulants-
A: Okay - thanks

A: 1st paragraph: missing dexmethylphenidate XR approved in children, adol and adults.
2nd paragraph, line 1: lisdexamfetamine package insert recently changed to 14 hour duration in adults
2nd paragraph, line 6:I'd be reluctant to use a weight base measure here as there is no clinically relevant concept in adult psychiatry for ADHD (with the exception atomoxetine)
3rd paragraph, line 4: is this an XR preparation? if so, mention it. If not, this preparation is good for 4-6 hours, not long acting, not indicated in adult ADHD in US.
A: Thanks – will check the information.

Second line psychotherapeutic agents-
Q: 1st paragraph, line 4: two studies in adults with effect sizes .35 and .4 The .6 must be the child study but I thought the effect size was .7. check this and clarify.
A: Will check this.

Q: Also in this line, strattera duration was this duration in child or adult study? clarify.
line 8: check this.
A: will check this

Q: I'm only aware of the Desipramine trial in adults, not an Imipramine trial.
last line needs clarification: and they are not approved to treat ADHD, except guanfacine extended release in children in US.
A: Will check this

Q: 2nd paragraph, line 2: Given that polypharm in the order of the day with adults with comorbidities, it may be helpful to mention the absence of inhibitory effects of MPH and AMPH on P450 enzymes. That's not to say there may not be pharmacodynamic interactions.
A: Good point – have added this

Q: last sentence: I’d clarify this sentence and mentioned the RCTs have not shown consistent support for the use of
complementary and alternative nutriceuticals.

A: We have clarified this

Coaching and CBT-
Q: 4th paragraph: It is worth noting that there are controlled trials with CBT (Safren) and Meta-cognitive therapy (Solanto) that have been positive. This shows the field is moving to demonstrate efficacy of specific therapies. also very good recent reference on psychotherapies in adult ADHD by M Weiss et al. can be added.
A: I agree – it looks as we were rather lazy with this section and referred all to a review paper that includes the mentioned papers. However we now expand this section to give a more positive awareness of developments in non-pharmacological treatments.

Prognosis-
Q: 1st paragraph,line 5: "The poor long term prognosis of untreated ADHD..."
A: Have clarified this

Level of interest An article of outstanding merit and interest in its field
Quality of written English Acceptable
Statistical review Yes, but I do not feel adequately qualified to assess the statistics.
A: We thank the reviewer for the positive comments. There were no statistical analyses in this paper so we were not sure why there is a recommendation for a statistical reviewer?