Journal of Central Nervous System Disease

EXPERT REVIEW

Atomoxetine in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. Systematic Review of Review Papers 2009–2011. An Update for Clinicians

Chris J. Bushe MBBS and Nicola Savill

Eli Lilly and Company Ltd, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL, UK.
Corresponding author email: bushe_chris@lilly.com

Abstract: Attention deficit/hyperactivity disorder (ADHD) is a common disorder and a plethora of new data has been published from clinical trials and national epidemiological databases in the last three years. In the United Kingdom Atomoxetine is currently the only licensed non-stimulant medication. As part of a systematic review of atomoxetine data Jan 2009–June 2011 formal searches found 750 citations. From these 13 met criteria for either review or systematic review papers and contained clinical data synthesis on atomoxetine. No individual review paper alone would be sufficient for clinicians to be updated at that time on all clinical aspects of atomoxetine data. The crucial data relating to clinical parity of atomoxetine and methylphenidate in trials and meta-analysis where relevant confounding biases are removed are not often discussed. Systematic review of complex data is critical for ADHD clinicians and will need regular updating due to the large volume of new data.

Keywords: ADHD, suicidality, summary of product characteristics, systematic review, review, atomoxetine

Journal of Central Nervous System Disease 2011:3 209–217

doi: 10.4137/JCNSD.S4391

This article is available from http://www.la-press.com.

Overview of ADHD

Attention deficit/hyperactivity disorder (ADHD) is not only a common neurodevelopmental disorder of childhood but one which currently has relatively few pharmacological options and limited psychosocial and behavioural interventions for treatment. Worldwide population prevalence rates are generally estimated to be around 5.3% with some geographical variability.[1] ADHD is associated with a range of clinical problems that translate into clear pragmatic endpoints that include low school grades, increased rates of accidents, substance abuse and expulsion from school.[2] In addition ADHD in almost 50% of cases is associated with comorbid psychiatric diagnoses that include conduct disorder, oppositional defiant disorder, autism spectrum disorders, anxiety and depression.

The role of review and specifically systematic review is becoming increasingly important in aiding information dissemination due to the increasing number of publications available via different media. Clinical data on any topic is being published in various media in increasing amounts and clinicians are unlikely to have the available time to read all the data in their specific area. Clinicians may hence depend upon data assimilation in the form of reviews. Reviews need to be complete to provide decision making tools and systematic review may in future become the benchmark for any data conclusion.[3] Pragmatically though not all reviews can be current and contain up-to-date publications which will reduce their external validity. In the 2-year period between 2009 and 2011, there were more than 750 publications on atomoxetine and our aim is to measure the number and quality of reviews, to establish both clinical utility and limitations of the data and to establish whether a single comprehensive review paper may meet clinicians' needs. To address this issue recent papers that meet the criteria as a review paper have been analysed using as a template a series of relevant clinical questions for which clinicians may require updated information and which still remain unanswered in child and adolescent ADHD.

Atomoxetine is currently the only non-stimulant medication licensed in the United Kingdom for the treatment of ADHD and has been available since 2004. The data from registration trials published between 2001 and 2005 provided an initial dataset however clinicians may feel it salient to review more recent clinical data that may provide additional clinical utility in the context of increased awareness, understanding and exposure to the medication. The purpose of this review is to evaluate some of the more recent data on atomoxetine published since 2009 and consider whether published reviews may provide clinicians with the totality of the available data, and also address pragmatic clinical questions.

ADHD is likely to assume greater focus in coming years with the advent of new medication options and the role of review papers on individual medications, particularly with regard to emerging clinical endpoints such as quality of life[4] and pragmatic endpoints such as mortality[5] may be important. The role of databases, such as the Nordic databases,[6] USA databases[5] and the United Kingdom UKGPRD[7] will provide data on endpoints that are not just limited to prescribing practice but critical safety and efficacy endpoints, that include discontinuation rates (accepted as a surrogate for effectiveness in schizophrenia in major trials),[7] mortality and long term cardiovascular outcomes. The development of databases over the last decade and their ability in individual countries to be cross-referenced to other databases has been a critical development for clinicians.

Methods

A search strategy was used to review all atomoxetine data published from January 2009 to June 2011. An initial PubMed search using atomoxetine as search term reported 245 citations. A more extensive search utilising all relevant and accessible databases found 750 individual citations. In this analysis, the authors have included data relating to child/adolescent ADHD only and which is published in English. We have also excluded all non-clinical data relating to neurobiology and neurochemistry and non-human data. Abstracts were reviewed and where relevant full clinical papers were obtained. We identified and have specifically reviewed all review papers to assess to what extent recent data and clinical implications have been addressed. To that extent we have included predominantly systematic reviews or reviews that contain synthesis of atomoxetine data. Definition of what constituted a review paper has no precise measurement. Our definition incorporated review papers in which a synthesis of atomoxetine data was provided with

evidence that there was some degree of systematic analysis and inclusion of all relevant data.

A series of pre-defined clinically relevant questions were selected and the review papers were evaluated on the degree and totality of the data available at that time to provide a clinical answer for prescribing clinicians. Our assumption was that clinicians may derive critical prescribing information and an updated literature synthesis from systematic review and review papers, and this format of data communication may be more pragmatic than having to access multiple individual data-sets. In addition, the Summary of Product Characteristics (SPC) for a medication provides the agreed data on safety and efficacy from the licensing authority, most commonly in Europe the European Medicines Evaluation Agency and as such represents the ultimate independent opinion on the totality of the dataset of a medication giving precise and categorical prescribing information that include monitoring and contraindications to use. The SPC in addition undergoes regular updates primarily to include new safety data. We have hence also evaluated the degree to which review papers are consistent with the SPC in giving comment and advice to clinicians.

On the basis of the above the following clinical questions were selected as to what degree the individual review papers addressed and provided a complete answer for where available:

1. What is the comparative efficacy of atomoxetine and methylphenidate?
2. What data is available on use of atomoxetine in patients with ADHD and comorbidities?
3. What might be considered relevant clinical endpoints in trials?
4. What is the trajectory of onset of response and how long should successful treatment be continued?
5. Are relevant and complete data on suicidality included in the reviews?

Results

A total of 13 review papers[4,8–19] were included, of which seven were either stated to be systematic reviews or were likely to meet the criteria as judged by the authors of this paper (Table 1). Search methodology was well described in only one systematic review.[8]

Five reviews specified atomoxetine as the sole drug of interest[9–12,14] of which one review considered atomoxetine in patients with ADHD and co-morbid conditions solely.[9] Five further reviews included a review of atomoxetine within a more generic review[13,15–17,19] and the remaining three, all systematic reviews, evaluated relevant and specific individual clinical questions, how long should medication be extended in ADHD management of adverse events from ADHD treatments and data on quality of life.[4,8,18]

The degree to which each review paper addressed the defined clinical questions is shown in Table 1 and briefly summarised below. For some reviews it was out of scope to address many of these clinical questions. Only two reviews correctly cited the full suicidality data set available at the time.[10,12] There was consistency with the atomoxetine SPC with regard to suicidality however one review stated that there is no systematic data on stimulant suicidal ideation/tendency rates in the public domain[8] and another did not cite the available comparative head to head data with stimulants.[18] The critical data not included was the comparative suicidality data from head to head trials between atomoxetine and methylphenidate which was published as a meta-analysis in 2008 in the same paper that reported atomoxetine suicidal events that is widely cited in most of the reviews.[20] This database reported no difference in rates between atomoxetine and methylphenidate (Maentzel-Haentzel incidence difference −0.12 (95% confidence interval—0.62–0.38; $P = 0.649$).[20] Critically though two reviews make the point that suicide related events are common in young people whom do not have ADHD and there is no compelling evidence that the observed event rate in ADHD treated cohorts is greater than in the general population.[8,18]

The comparative efficacy of atomoxetine and stimulants was addressed to some extent in 10 out of 11 relevant reviews concluding the superiority of OROS MPH over atomoxetine and predominantly citing Newcorn 2008,[21] Kemner 2005[22] (a 3-week study) and Faraone 2006[23] (an indirect meta-analysis). The two reviews that did not address this topic were specific review topics outside of this area of interest.[9,18] Only four review papers however discuss the Newcorn, 2008 findings that 43% of non-responders to methylphenidate respond to atomoxetine, and 42% vice versa,[10,13,14,16,21] and the implication that individual patients may have differential response to these two agents. There is a critical confounding bias that

Table 1. Critical questions addressed by reviews that include atomoxetine data.

Author	Type of review	Comparative efficacy	ADHD and comorbidity
Buitelaar[16]	Review	Less effective than OROS MPH. Review is of stimulant data	x
Coghill[4]	Systematic review	No published RCTs on QOL with MPH. Data are observational/ open label	ODD
Daughton[9]	Review	Less effective than stimulants. Meta-analysis cited as poster APA	First line in anxiety
Dell'Agnello[15]	Can be considered a systematic review although no methodology stated	x	Specific purpose of review. ASD, tics/tourettes, anxiety/ depressive symptoms, ODD
Dopheide[19]	Review	Less effective than stimulants/OROS based on effect sizes	Tics/Tourettes and anxiety
Garnock-Jones[12]	Can be considered systematic review with no clear methodology section	Less effective than OROS MPH	Anxiety, tics depression, ODD and autism. Efficacy similar with no worsening
Garnock-Jones[11]	Review	Less effective than OROS MPH	Helpful in comorbid conditions
Graham[18]	Systematic (not stated)	x	Tics/Tourettes/SUD epilepsy
Hammerness[10]	Systematic review	States atomoxetine as less effective than OROS MPH based on effect sizes	ODD, tics, anxiety, MDD/PDD
May[13]	Systematic (not stated)	States atomoxetine as less effective than stimulants/OROS MPH. Points out data on differential response rates to MPH or ATX. Confounding bias of excluding MPH non-responders is discussed	Tics, anxiety, ODD, depression
Van de Loo-Neus[8]	Systematic	Compares medicationeffect sizes and refers to 2 studies (Newcorn 2008; Michelson 2002)	Tics, anxiety, ODD and ASD
Vaughan[14]	Review	Compares medication effect sizes and describes increased effect size of atomoxetine in naive pts. References Newcorn 2008	ODD, tics/Tourettes, anxiety, MDD
Wilens[17]	Review	x	"particularly useful" tics and anxiety

Relevant clinical endpoints	Onset of action/duration of treatment	Suicidality
x	X	No data
X	X	No data
x	Peak efficacy 2–6 weeks	Does not include mph data from the meta-analysis, untreated ADHD rates or general population
x	x	Does not include mph data from the meta-analysis or general population but does link comorbidities with ADHD with an increased likelihood of suicidal behaviours
x	Delayed onset (2–4 wks)	Does not include MPH data from the meta-analysis, untreated ADHD rates or general population
Improved relapse rates compared with placebo	12 weeks treatment superior to 6 weeks. Efficacy takes up to 8 weeks. Efficacy maintained for up to 2 years	Includes ATX and mph data from the meta-analysis but not general population rates or those with untreated ADHD
X	X	Does not include mph data from the meta-analysis, untreated ADHD rates or general population
Long term safety	x	Does not include mph data from the meta-analysis, untreated ADHD rates or general population
Improved grades	Efficacy not maximal until 12 weeks	Includes data on MPH
Relapse prevention	No need for ATX dose escalation in studies up to 60 months. Long term (8yrs) safety data in adolescents consistent with acute studies. Efficacy in 2–8 weeks	Does not include MPH data from the meta-analysis, untreated ADHD rates or general population
Long term pragmatic outcomes	Specific focus of the review	Does not include mph data from the meta-analysis, untreated ADHD rates or general population
x	Full effect 6–8 weeks	Does not include mph data from the meta-analysis, untreated ADHD rates or general population
x	x	Does not include mph data from the meta-analysis, untreated ADHD rates or general population

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; ASD, autism spectrum disorders; MDD, major depressive disorder; X, not addressed within review; ODD, oppositional defiant disorder; MPH, methlyphenidate; ATX, atomoxetine; OROS, osmotic release oral system; PDD, pervasive developmental disorder; SUD, substance use disorder; QOL, quality of life; RCT, randomised controlled trial; APA, American Psychiatric Association.

previous stimulant non-responders were excluded from Newcorn 2008.[21] Although this was discussed in that paper it is not fully addressed in any review and is mentioned only in a single recent review.[13] Most reviews include the Newcorn 2008 treatment naïve data analysis and state that the response rates for OROS MPH and atomoxetine were not significantly different, $P = 0.43$[16] however this is not reviewed in the context of this cohort having critically removed the confounding bias of having excluded previous stimulant non-responders. The two atomoxetine studies in treatment naïve cohorts that report high effect sizes (0.8 and 1.3)[24,25] are only fully presented in one review.[12]

The role of atomoxetine in patients with comorbidities was discussed in varying amounts of detail in all but one of the 13 reviews, (Buitelaar 2010[16] reviewed stimulant data) concluding broadly that atomoxetine may have a specific role in such patients as evidence was suggestive that the efficacy of atomoxetine remained consistent with little evidence for worsening of such comorbidities.

What might be considered relevant clinical endpoints were discussed in two reviews, one for efficacy[8] and the other safety.[18] The clinical question of when clinical response to atomoxetine commences, when maximal efficacy may be seen and for how long treatment should be continued was discussed in six reviews, with inconclusive and varied findings. In terms of time to peak efficacy of atomoxetine conclusions varied from 2–6 weeks[15] up to 12 weeks.[10,12] Most reviews concluded that long term data were sparse, especially in the area of quality of life[4] and although concluding that efficacy was maintained for 2 years[12] there were minimal clinical recommendations on length of usage other than this should be an "individual patient decision".[8]

Discussion

From 2009 until June 2011 we found 13 papers that could be classified as review papers that contained a clinical data synthesis on atomoxetine, of which five were specific for atomoxetine. In general terms each of our clinical questions were addressed in most review papers other than the identification of future pragmatic endpoints outside of clinical rating scales; however most of the more recent atomoxetine data was not included in many of these reviews. When analysing the review papers it cannot be a precise science to fully determine the dataset available at the time of publication as for many journals the publication process may be 6–12 months. It is encouraging to observe a trend towards journals seeking high quality systematic reviews that potentially may address important patient outcomes in disorders that will include ADHD[3] which may aid clinical decision making if a full and complete data analysis is provided. There remain many questions unanswered however and clinicians may be further informed by additional long term clinical data. In general terms though, the 13 reviews are high quality publications with the caveat that no single review could be considered the sole publication for a clinician to be totally updated on current atomoxetine data.

Our major conclusion was that some, though not all, of the recent atomoxetine data is included in the reviews due in part, though not totally, to the timing of publication. We found reasonable evidence that relevant data had not been included in some of the reviews when available with particular regard to suicidality and the treatment naïve atomoxetine dataset.

The most complete atomoxetine reviews are the excellent Garnock-Jones 2009 and May 2010 reviews[12,13] which can probably be classed as systematic reviews in many regards.[3] Neither however is complete in their data inclusion. There is an absence of comment in many of the reviews on the three treatment naïve studies, maybe due to the time of publication, two randomised, placebo-controlled and the other an open-label study[24–26] relating both to the linearly increasing effect size[25] and full interpretation of these data. This is a critical data set. Not only are effect sizes for ADHD-RS greater in these cohorts (0.8–1.3) but critically in the open-label study significant improvement was measured in various non-verbal executive functions.[26] The Montoya 2010 study reports a linearly increasing effect size over 12 weeks with no evidence of plateau that raises a question as to the time of maximal efficacy with atomoxetine.[25] In addition comparative data with methylphenidate was reported in 2008 from the treatment-naïve cohort of a large RCT[21] showing the same effect size (MPH 1.0, ATX 0.9). In comparing treatment naïve data the confounding bias of any previous treatments is removed. This is a critical confounding bias as previous stimulant failure is an exclusion criterion for most head to

head methylphenidate and atomoxetine studies. This potential confounding bias is only discussed in a single review.[13] These data when combined with the recent non-inferiority meta-analysis that included all direct comparative atomoxetine and methylphenidate studies of at least 6 weeks duration, and concluded no difference in ADHD IV RS between drugs,[27] challenge previously held beliefs that methylphenidate has been proven to have a significantly greater effect size. This view is still held in many of the review papers despite emergence of these new data.

The aspect of suicidality is often raised in atomoxetine reviews, however only two reviews include data on the published meta-analysis of suicidality in comparative trials between atomoxetine and methylphenidate finding no differences. Furthermore in terms of completed suicides no review is able to include the mortality data from the UK GPRD analysis in 2009 that reported on seven deaths in patients receiving ADHD medications, none on atomoxetine and two suicides in patients receiving methylphenidate.[28] This data set is derived from an analysis of all deaths in patients prescribed ADHD treatment medications over the period 1993–2006 in the UK using the UKGPRD. Although not within the scope of our systematic review the SPCs for methylphenidate and atomoxetine both mandate regular monitoring for symptoms of suicidality and the presence of suicidal tendencies remains a contraindication for methylphenidate usage. The UKGPRD analysis was also salient for what was not found. The initial protocol for this analysis sought to measure the number of sudden death cases in the UK during this 13-year period on subjects receiving ADHD medications. Their analysis however found that there were no cases of sudden death allowing the analysis to be broadened to mortality of all causes.

The question of how long medication should be continued for was the specific topic for one review,[8] concluding that treatment needed to be decided on an individual basis due to lack of long term clinical data. The time for onset of full efficacy with atomoxetine was addressed in some reviews with contrasting conclusions. One review concluded full efficacy develops between 2–6 weeks of treatment,[15] with other reviews suggesting 12 weeks.[10,12] The totality of the evidence predominantly from the two treatment naïve studies[24,25] is supportive of the need for 12 weeks treatment to observe maximal efficacy.

The large quantity of atomoxetine data published over the last 2 years makes many reviews complex to interpret. Many reviews have been published before some of these seminal data could be included and for a clinician no single review provides the totality of available data at that time.

Currently clinicians must incorporate new emerging data on clinical endpoints that they may not be so familiar with,[29] exampled by complex quality of life rating scales, and the many guidelines[30,31] to make clinical decisions. Clinicians in the future will remain most likely unable to appraise and assimilate the vast body of data that will continue to emerge and will rely upon systematic review increasingly to help them answer clinical questions and improve patient outcomes. The expectation will be that there may be a greater number of focused systematic reviews.

Conclusion

Over the last 2 years there have a number of high-quality reviews and systematic reviews that will help clinicians to make critical patient outcome decisions. In particular the European guidelines on management of adverse effects produced by the guidelines group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) can be recommended[18] and the data analysis on treatment length required for ADHD patients.[8] The trend to move away from pure review papers to systematic reviews is encouraging.[3] By doing so the more recent atomoxetine data will be critically appraised and included in future reviews. Only a few of the reviews are able to speculate on future trials needed to inform clinicians regarding the relative efficacy of the ADHD medications. The bias towards methylphenidate of excluding previous stimulant failures can be addressed in treatment naïve cohorts. The recent evidence is supportive when these biases are addressed of little difference in effect size between these two agents.

Our defined clinical questions will further benefit from future longer term clinical trials. The value of epidemiological database research and longer term open label studies in larger cohorts needs further evaluation and may eventually provide some of the answers that our patients require.

Systematic review may be a clinical tool to aid clinicians in their knowledge. Our findings suggest that with the volume of emerging clinical data

there may be a need for regular updating of both reviews and systematic reviews. A clinician reading a single review is unlikely to be appraised of all the data needed to inform patient medication decisions at present. Fortuitously the trend towards free open access publishing continues and many of our cited references are available to download free of charge.

With a plethora of published data on ADHD emerging, and a likelihood of more medications licensed in ADHD, there is need for regular systematic reviews not only on specific ADHD medications but on crucial aspects of outcomes. Pragmatic outcomes are becoming measurable (mortality and cardiovascular outcomes as examples).[5] Further systematic reviews can address the longer term safety and outcomes of individual ADHD medications. Finally, in the current era of internet based data dissemination, the role of the SPC as a regularly updated document from the regulatory agencies, needs to be fully compared with other sources of independent data and guidance for clinicians.[18,30,31] These guidelines include both European and national guidance on ADHD management and prescribing.[18,30,31] Such a review may address the most appropriate data sources to help clinicians implement patient care.

Disclosures

CB, NS are employees of Eli Lilly and Company who manufacture atomoxetine.

References

1. Polanczyk G, de Lima MS, Horta BL, Biedrman J, Rohde LA. The Worldwide Prevalence of ADHD: A Systematic Review and Meta-regression Analysis. *Am J Psych*. 2007;164:942–8.
2. Coghill D, Soutullo C, d'Aubuisson C, et al. Impact of attention-deficit/hyperactivity disorder on the patient and family: results from a European survey. *Child Adolesc Psychiatry Mental Health*. 2008;2:31.
3. Bushe CJ. Systematic reviews—A perspective on benefits and concerns in 2011. Safe, sound and sorted? *Int J Clin Pract*. Sep 2011;65(9):921–2.
4. Coghill D. The impact of medications on quality of life in attention deficit hyperactivity disorder. A systematic review. *CNS Drugs*. 2010;24(10): 643–66.
5. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. *Pediatrics*. 2011; 127(6):1102–10.
6. Zoëga H, Furu K, Halldórsson M, Thomsen PH, Sourander A, Martikainen JE. Use of ADHD drugs in the Nordic countries: a population-based comparison study. *Acta Psychiatr Scand*. 2011;123(5):360–7.
7. McCarthy S, Asherson P, Coghill D, et al. Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. *Br J Psych*. 2009;194:273–7.
8. Van de Loo-Neus GH, Rommelse N, Buitelaar JK. To stop or not to stop? How long should medication treatment of attention-deficit hyperactivity disorder be extended? *Eur Neuropsychopharmacol*. 2011;21:584–99.
9. Dell'Agnello G, Zuddas A, Masi G, Curatolo P, Besana D, Rossi A. Use of Atomoxetine in Patients with Attention-Deficit Hyperactivity Disorder and Co-Morbid Conditions. *CNS Drugs*. 2009;23(9):739–53.
10. Hammerness P, McCarthy K, Mancuso E, Gendron C, Geller D. Atomoxetine for the treatment of attention deficit/hyperactivity disorder in children and adolescents-A review. *Neuropsychiat Dis Treat*. 2009;5:215–26.
11. Garnock-Jones KP, Keating GM. Spotlight on atomoxetine in attention deficit hyperactivity disorder in children and adolescents. *CNS Drugs*. 2010; 24(1):85–8.
12. Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Paediatr Drugs*. 2009;11(3):203–6.
13. May DE, Kratochvil CJ. Attention-deficit hyperactivity disorder: recent advances in paediatric pharmacotherapy. *Drugs*. 2010;70(1):15–40.
14. Vaughan B, Fegert J, Kratochvil CJ. Update on atomoxetine in the treatment of attention-deficit/hyperactivity disorder. *Expert Opin Pharmacother*. 2009;10(4):669–76.
15. Daughton JM, Kratochvil CJ. Review of ADHD pharmacotherapies: advantages, disadvantages, and clinical pearls. *J Am Acad Child Adolesc Psychiatry*. 2009;48(3):240–8.
16. Buitelaar J, Medori R. Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: a review of the potential benefits of long-acting stimulants. *Eur Child Adolesc Psychiatry*. 2010;19(4):325–40.
17. Wilens TE, Spencer TJ. Understanding attention-deficit/hyperactivity disorder from childhood to adulthood. *Postgrad Med*. 2010;122(5):97–109.
18. Graham J, Banaschewski T, Buitelaar J, et al. European Guidelines on Managing Adverse Effects of Medication for ADHD. European Child and Adolescent Psychiatry. *Eur Child Adolesc Psychiatry*. 2011;20(1):17–37.
19. Dopheide JA, Pliskza SR. Attention-deficit disorder: an update. *Pharmacotherapy*. 2009;29(6):656–79.
20. Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior-events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry*. 2008;47(2):209–18.
21. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *Am J Psychiatry*. 2008;165(6):721–30.
22. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. *Adv Ther*. 2005;22(5):498–512.
23. Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. *Med Gen Med*. 2006; 8(4):4.
24. Svanborg P, Thernlund G, Gustafsson PA, Hagglof B, Poole L, Kadesjo B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naïve Swedish children and adolescents. *Eur Child Adolesc Psychiatry*. 2009;18(4):240–9.
25. Montoya A, Hervas A, Cardo E, et al. Evaluation of atomoxetine for first-line treatment of newly diagnosed, treatment-naïve children and adolescents with attention deficit/hyperactivity disorder. *Curr Med Res Opin*. 2009; 25(11):2745–54.
26. Gau SS, Shang CY. Improvement of executive functions in boys with attention deficit hyperactivity disorder: an open-label follow-up study with once-daily atomoxetine. *Int J Neuro psycho pharmacol*. 2010;13(2):243–56.
27. Hazell PL, Kohn MR, Dickson R, Walton RJ, Granger RE, van Wyk GW. Core ADHD Symptom Improvement With Atomoxetine Versus Methylphenidate: A Direct Comparison Meta-Analysis. *J Atten Disord*. September 28, 2010. [Epub ahead of print.]
28. McCarthy S, Cranswick N, Potts L Taylor E, Wong IC. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. *Drug Saf*. 2009;32(11): 1089–96.

29. Prasad S, Harpin V, Poole L, et al. A multi-centre, randomised, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Curr Med Res Opin*. 2007;23(2):379–94.
30. NICE. Attention deficit hyperactivity. The NICE guideline on diagnosis and management of ADHD in children, young people and adults. National Clinical Practice Guideline no. 72. 2009. Available at: http://www.nice.org.uk/nicemedia/live/12061/42060/42060.pdf. Accessed January 15, 2011.
31. Banaschewski T, Coghill D, Santosh P, et al. Long-acting medications for the hyperkinetic disorders A systematic review and European treatment guideline. *Eur Child Adolesc Psychiatry*. 2006;15:476–95.