Polypharmacy with antidepressants in children and adolescents

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Abstract
The aim of this study was to review current epidemiological data on the use of antidepressants in co-prescription with other psychotropic drugs in children and adolescents, as well as available efficacy and safety information. A Medline search from inception until February 2012 was performed to identify epidemiological and clinical studies, reviews and reports containing potentially relevant information on polypharmacy with antidepressants in young people. There has been an increase in polypharmacy in children and adolescents involving antidepressants in recent years. Antidepressants have become one of the drug classes most frequently prescribed in combination and are commonly co-prescribed with stimulants and antipsychotics. Most information regarding efficacy and safety of polypharmacy patterns was provided by case series and open-label studies. Efficacy studies gave some support for the use of a combination of antidepressants and antipsychotics in the management of refractory obsessive-compulsive disorder and some residual symptoms in major depressive disorder. Even less empirical support was found for a combination of stimulants and antidepressants in co-morbid attention deficit hyperactivity disorder and mood or anxiety disorders. Adverse events were similar to those found with individual medication groups, with severe adverse events mostly reported by individual case reports. The use of polypharmacy with antidepressants has become a regular practice in clinical settings. Although there is still little efficacy and safety information, preliminary evidence points to the potential clinical usefulness of some polypharmacy patterns. Further research on patients with co-morbidities or more severe conditions is needed, in order to improve knowledge of this issue.

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Introduction
Recent prevalence studies reveal that depressive and anxiety disorders are common among young people, with figures ranging 10–25% of community samples and that even the severe forms of these disorders affect up to 6% of young people aged 13–18 yr (Costello et al. 2003; Merikangas et al. 2010). These disorders are associated with high morbidity and functional impairment (Puig-Antich et al. 1985; Kendall et al. 2010; Nagar et al. 2010), as well as increased mortality (Olsson et al. 2003a) in children and adolescents, which underscores the need of their early recognition, identification and effective management. Even though there has been a recent increase in evidence for the use of antidepressants in childhood psychiatric disorders, much of their current use is still off-label. Thus, one recent study found that only 9.2% of visits in US ambulatory-care settings in which antidepressants were prescribed to children and adolescents were related to Food and Drug Administration-approved indications (Lee et al. 2012).

Furthermore, the use of selective serotonin reuptake inhibitors (SSRIs) in paediatric patients remains a matter of debate, as SSRIs have shown little difference in efficacy compared with placebo in the treatment of paediatric depression (Cheung et al. 2005; Bridge et al. 2007). In fact, current guidelines recommend psychotherapy as the first step for management of mild and moderate depressive episodes in paediatric patients, leaving the use of antidepressants for severe patients or those who fail to respond to psychotherapy (National Institute for Health and Clinical Excellence, 2005a; Birmaher et al. 2007). Meta-analyses have consistently detected the greatest efficacy in clinical trials for fluoxetine, both in children and adolescents (Hetrick et al. 2007; Usala et al. 2008), with weaker evidence supporting the use of citalopram and sertraline in adolescent depression (Wagner et al. 2003, 2004). Tricyclic antidepressants (TCAs) and venlafaxine have not however proved to be efficacious for paediatric depression (Moreno et al. 2006). While the efficacy of SSRIs is greater for the treatment of anxiety and...
obsessive-compulsive disorder (OCD) than for the treatment of depression in children and adolescents (Bridge et al. 2007), alternative strategies to antidepressant treatment are often needed. Although generally well tolerated, SSRIs have been associated with an increased risk of behavioural activation and worsening of suicidal ideation in paediatric depression patients (Hammad et al. 2006). Also, while the relationship of SSRIs to suicide remains controversial (Olsson et al. 2003a; Dubicka et al. 2006; Gibbons et al. 2006), regulatory warnings may have slowed the increasing trend for antidepressant prescription observed through the mid-2000s (Nemeroff et al. 2007; Libby et al. 2009).

Given the severity of paediatric mood and anxiety disorders and their psychosocial and functional consequences, clinical practice demands the development of complementary approaches for difficult cases, such as combining antidepressants with other psychotropic drugs. This clinical need is increased in patients with comorbidities or more severe conditions such as psychotic depression or treatment-resistant depression or OCD. Polypharmacy can be defined as the ‘administration of many drugs together’ (Saunders, 2007), which may target the same or different emotional or behaviour syndromes. Despite the different methodological approaches and differences in magnitude depending on the country, there has been a consistent increase in the use of polypharmacy involving psychotropic drugs in paediatric patients in recent years (Safer et al. 2003; Comer et al. 2010).

Polypharmacy in paediatric patients with major depressive disorder (MDD) has also experienced a substantial increase (almost six-fold between 1996 and 2005; McIntyre and Jerrell, 2009) and the use of antidepressants in combination with other psychopharmacological treatments has also markedly grown in recent years, becoming a regular practice (Comer et al. 2010). This practice has even been supported by clinical guidelines, although there is little evidence derived from child studies and most safety information comes from efficacy studies in monotherapy with far less data available for combination treatments. Hence, polypharmacy with antidepressants is recommended for the treatment of a wide range of disorders, such as depression with psychotic features, treatment resistant depression or OCD and attention deficit hyperactivity disorder (ADHD) with co-morbid depressive or anxiety disorders (American Academy of Children and Adolescent Psychiatry, 1998; Pliszka et al. 2006; Birmaher et al. 2007; Hughes et al. 2007), although most clinical guidelines explicitly acknowledge the lack of empirical support for such recommendations and the need for further research on polypharmacy.

Although previous studies have focused on polypharmacy in minors (Safer et al. 2003) or in paediatric patients with a diagnosis of MDD (McIntyre and Jerrell, 2009) there are, to our knowledge, no published studies specifically focusing on polypharmacy with antidepressants in children and adolescents. The widespread use of combinations of antidepressant and other medications and the potential risks in this vulnerable population justify the study of this practice. The current study aims to review the frequency of use of polypharmacy with antidepressants in children and adolescents, the efficacy data supporting its use and the safety issues associated with it.

Method

A Medline search from inception until February 2012 was performed using the following key words as search terms: polypharmacy; antidepressant; SSRI; serotonin; psychotropics; depression; paediatric; child; adolescent; multiple; concomitant and combination as well as the names of all individual antidepressants combined with the main individual compounds of each drug group [antipsychotics, stimulants and mood stabilizers (MSs)]. This search was supplemented by manual review of the reference lists from relevant articles and reviews. Inclusion criteria: all papers providing information on frequency of use of polypharmacy involving antidepressants or assessing or reporting efficacy and/or safety data on combination patterns involving antidepressants in patients aged 0–19 yr were systematically reviewed. Given the expected scarcity of specific studies on this topic, we decided to perform an exhaustive search of the literature, thus including studies of differing methodological quality. Randomized controlled trials (RCT), naturalistic studies, open trials, chart reviews and case series comprising ≥4 cases assessing the combination of antidepressants with other psychotropic drugs in paediatric patients were systematically reviewed for efficacy and safety data. Individual case reports on polypharmacy with antidepressants (Alessi and Bos, 1991; Bussing and Levin, 1993; Budman et al. 1995; Burke et al. 1995; Cruz-Flores et al. 1995; Daniel et al. 1996; Took and Buck, 1996; Feeney and Klykylo, 1997; Sallee et al. 2000; Aldurra and Crayton, 2001; Ghaziuddin et al. 2001; Padla, 2001; Ickowicz, 2002; Ercan et al. 2003; Pathak et al. 2004; George et al. 2005; Curtis and Richards, 2007; Coskun and Zoro glu, 2008; Schertz and Steinberg, 2008; Dadic-Hero et al. 2009; Ozcan and Selimoglu, 2009; Park and Jung, 2010; Mahapatra et al. 2011) and case series including <4 cases (Walter et al. 1998; Wehr and Namerow, 2001; Owley et al. 2002; Duggal et al. 2003; Srivastava et al. 2005; Good, 2006; Oner and Oner, 2008) were mainly reviewed for general safety information. No exclusion criteria based on diagnosis or other methodological issues were applied.

Results

Use of polypharmacy involving antidepressants

Frequency of use

Although there is little specific data regarding the use of polypharmacy with antidepressants, in recent years there
has been an increasing trend for its use (Rushton and Whitmire, 2001; Comer et al. 2010). Most studies report that antidepressants belong to the drug subclasses most frequently prescribed in combination (Olfson et al. 2002; Martin et al. 2003; dosReis et al. 2005; Duffy et al. 2005) and are included in 35–61% of the combination regimes prescribed by child psychiatrists (Sourander, 2004; Duffy et al. 2005; Dean et al. 2006). Among antidepressant users, rates of polypharmacy have been reported to range 16–34% (Schirm et al. 2001; Olfson et al. 2002). Although SSRIs are the class most frequently involved in polypharmacy with antidepressants (Sourander, 2004; Hunkeler et al. 2005; Dean et al. 2006), bupropion seems to be increasing in popularity, with one study in the USA finding it to be the most frequently co-prescribed antidepressant in office-based practice (Comer et al. 2010). Table 1 provides a summary of the frequency of use of polypharmacy involving antidepressants and the most frequent combinations.

Polypharmacy rates in paediatric patients treated for MDD were found to significantly increase from 7.9% in 1996 to 45% in 2005, with the greatest rate of change between 1997 and 2003 (McIntyre and Jerrell 2009). On the other hand, patients with mood disorders are involved in more than half the paediatric visits to office-based physicians in which multi-class psychotropic treatment is prescribed, as compared to only one-sixth of single-class psychotropic visits (Comer et al. 2010). Although the most frequently prescribed combinations in children treated for MDD vary from year to year, there seems to be a shift from combining stimulants with antidepressants towards combining antidepressants with antipsychotics, as well as antipsychotics with MSs and stimulants (McIntyre and Jerrell, 2009).

Similarly, polypharmacy rates in OCD have been reported as 30% (Geller et al. 1995), whereas 63–68% of young people treated for bipolar disorder (BD) receive polypharmacy (Moreno et al. 2007; Geller et al. 2010) and antidepressants are frequently involved in polypharmacy regimens. Thus, 23.6% of children and adolescents with BD receive antidepressants in combination with MSs, and 16.7% in combination with antipsychotics (Moreno et al. 2007). High rates of concomitant use of stimulants and antidepressants in young people with BD have also been reported, probably due to the high prevalence of reported co-morbid BD and ADHD in some settings (Geller et al. 2010).

Efficacy

Most of the retrieved articles assessed polypharmacy patterns involving SSRIs. No studies evaluating polypharmacy with bupropion were found whereas only a small two-case series was found for the combination of venlafaxine and lithium (Walter et al. 1998). Due to the potential clinical benefit of the combination, we included OCD studies assessing polypharmacy involving clomipramine, as well as two studies assessing the combination of TCAs with lithium for management of treatment-resistant MDD. Those two studies were considered clinically relevant for this review, since lithium has been recommended as an augmenting strategy for treatment-resistant paediatric MDD by clinical guidelines (Hughes et al. 2007), but no studies assessing lithium augmentation of SSRIs were found. However, other articles assessing combination patterns involving TCAs were not included, given that they play a lesser role in the management of paediatric depressive and anxiety disorders and most of those patterns have been previously reviewed elsewhere (Safer et al. 2003).

Only four of the studies assessing polypharmacy patterns involving antidepressants were RCT. The rest of the retrieved articles were open trials, naturalistic studies and case series (see Table 2).

Treatment-resistant depression

Two case series comprising a total of 12 patients assessing the addition of quetiapine to SSRIs reported improvement in some residual symptoms with the combination, mainly for sleep disorders and self-harming behaviours (Pathak et al. 2005; Good, 2006). One open-label study, one chart review and one small case series reported a
### Table 1. Frequency of use of polypharmacy involving antidepressants (ADs) in children and adolescents and most frequent combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population sample</th>
<th>Design</th>
<th>Dates</th>
<th>Age (yr)</th>
<th>Patients taking psychotropic drugs who receive polypharmacy involving ADs</th>
<th>Patients taking ADs who receive ADs in polypharmacy regimens</th>
<th>Psychotropic combination patterns involving the use of ADs</th>
<th>Most frequent combinations involving ADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>USA</td>
<td>National study.</td>
<td>Nationally representative surveys.</td>
<td>1996†</td>
<td>≤ 18</td>
<td>6490 N. R.</td>
<td>33.7% N. R.</td>
<td>68% of multi-class COMB.</td>
<td>AD + Stim.</td>
</tr>
<tr>
<td>Olsson et al. (2002)</td>
<td>USA</td>
<td>National study.</td>
<td>Nationally representative surveys.</td>
<td>1996–2007</td>
<td>≤ 18</td>
<td>27 979 13.29% of visits where a psychotropic drug was prescribed.</td>
<td>N. R.</td>
<td>AD + ADHD drugs: 7.3% of psychotropic visits. AD + AP: 5% AD + MS: 2.9% AD + sedative: 1.93% AD + sedative: 10% of COMB. AD + AP: 10% AD + AD: 6.7% of AD users. 5.6% used more than one AD subclass.</td>
<td>AD + ADHD drugs: 7.3% of psychotropic visits. AD + AP: 5% AD + MS: 2.9% AD + sedative: 1.93% AD + sedative: 10% of COMB. AD + AP: 10% AD + AD: 6.7% of AD users. 5.6% used more than one AD subclass.</td>
</tr>
<tr>
<td>Comer et al. (2010)</td>
<td>Germany</td>
<td>National study.</td>
<td>Nationally representative survey (KiGGS).</td>
<td>2003–2006</td>
<td>0–17</td>
<td>17 450 N. R.</td>
<td>N. R.</td>
<td>AD + sedative: 10% of COMB. AD + AP: 10% AD + AD: 6.7% of AD users. 5.6% used more than one AD subclass.</td>
<td>AD + sedative: 10% of COMB. AD + AP: 10% AD + AD: 6.7% of AD users. 5.6% used more than one AD subclass.</td>
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<tr>
<td>Koelch et al. (2009)</td>
<td>Germany</td>
<td>National study.</td>
<td>Nationally representative survey (KiGGS).</td>
<td>2003†</td>
<td>0–19</td>
<td>279 083 N. R.</td>
<td>N. R.</td>
<td>AD + sedative: 10% of COMB. AD + AP: 10% AD + AD: 6.7% of AD users. 5.6% used more than one AD subclass.</td>
<td>AD + sedative: 10% of COMB. AD + AP: 10% AD + AD: 6.7% of AD users. 5.6% used more than one AD subclass.</td>
</tr>
<tr>
<td>Fegert et al. (2006)</td>
<td>Germany</td>
<td>Health insurance organization. National study.</td>
<td>Analysis of AD prescriptions and administrative claims data.</td>
<td>1999</td>
<td>0–19</td>
<td>37 760 N. R.</td>
<td>15.7% N. R.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
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<tr>
<td>Schirm et al. (2001)</td>
<td>Netherlands</td>
<td>Regional study.</td>
<td>Study of pharmacy claims database.</td>
<td>2002</td>
<td>0–19</td>
<td>75 109 N. R.</td>
<td>N. R.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
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<tr>
<td>Faber et al. (2005)</td>
<td>Netherlands</td>
<td>Regional study.</td>
<td>Study of pharmacy claims for stimulants and ADs.</td>
<td>1999</td>
<td>0–19</td>
<td>275 949 N. R.</td>
<td>N. R.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
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<tr>
<td>dosReis et al. (2005)</td>
<td>USA</td>
<td>Medicaid and SCHIP. Regional study.</td>
<td>Analysis of administrative data of all enrollees.</td>
<td>1999</td>
<td>0–19</td>
<td>275 949 N. R.</td>
<td>N. R.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
<td>AD + stim: 1.8% of patients on Stim.</td>
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<tr>
<td>Martin et al. (2003)</td>
<td>USA</td>
<td>State Medicaid population. Regional study.</td>
<td>Cross-sectional study of administrative and pharmacy data.</td>
<td>1998–1999</td>
<td>≤ 18</td>
<td>196 505 N. R.</td>
<td>N. R.</td>
<td>AD + AP: 21.9% of COMB. AD + Stim: 15.1% AD + α2 agonist: 8.7% AD + MS: 6.4% AD + anxiolytic: 5.4%</td>
<td>AD + AP: 21.9% of COMB. AD + Stim: 15.1% AD + α2 agonist: 8.7% AD + MS: 6.4% AD + anxiolytic: 5.4%</td>
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<tr>
<td>Authors</td>
<td>Country</td>
<td>Region</td>
<td>Study Type</td>
<td>Data Source</td>
<td>Year</td>
<td>N</td>
<td>SSRI+Stim</td>
<td>SSRI+other AD</td>
<td>SSRI+SGA</td>
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<td>Hunkeler et al. (2005)</td>
<td>USA</td>
<td>Kaiser Permanenten Insurance, Regional study.</td>
<td>Pharmacy database including all out-patient prescriptions.</td>
<td>2003†</td>
<td>5–17</td>
<td>549 000</td>
<td>N. R.</td>
<td>N. R.</td>
<td>N. R.</td>
</tr>
<tr>
<td>Rushton and Whitmire (2001)</td>
<td>USA</td>
<td>Medicaid, Regional study.</td>
<td>Analysis of prescription claims for SSRI or Stim.</td>
<td>1998†</td>
<td>1–19</td>
<td>581 088</td>
<td>N. R.</td>
<td>N. R.</td>
<td>N. R.</td>
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<td>Special populations</td>
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<tr>
<td>Zito et al. (2008)</td>
<td>USA</td>
<td>Medicaid patients in foster care, Regional study.</td>
<td>Computerized claims data from a random sample of medicated youth in foster care.</td>
<td>7/2004</td>
<td>0–19</td>
<td>472</td>
<td>45.8%</td>
<td>80.6%</td>
<td>63.16%</td>
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<tr>
<td>Psychiatric settings</td>
<td></td>
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<tr>
<td>Duffy et al. (2005)</td>
<td>USA</td>
<td>Out-patients + in-patients, National sample.</td>
<td>Cross-sectional survey of APA psychiatrists.</td>
<td>1997–1999</td>
<td>2–17</td>
<td>392</td>
<td>N. R.</td>
<td>N. R.</td>
<td>60.9%</td>
</tr>
<tr>
<td>Dean et al. (2006)</td>
<td>Australia</td>
<td>Out-patients + in-patients, One CAMHS.</td>
<td>Retrospective chart review of all charts in the CAMHS.</td>
<td>4/2002–9/2003</td>
<td>2–17</td>
<td>248</td>
<td>In-patients: 28.7% (SSRIs) Out-patients: 28.12%</td>
<td>In-patients: 46.3% of those using SSRIs. Out-patients: 42.8% of those using AD. In-patients: 56.8% (SSRIs). Out-patients: 100%.</td>
<td></td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Population sample</td>
<td>Design</td>
<td>Dates</td>
<td>Age (yr)</td>
<td>n</td>
<td>Patients taking psychotropic drugs who receive polypharmacy involving ADs</td>
<td>Patients taking ADs who receive ADs in polypharmacy regimens</td>
<td>Psychotropic combination patterns involving the use of ADs</td>
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<tr>
<td>Staller et al. (2005)</td>
<td>USA</td>
<td>Out-patients. 8 out-patient locations.</td>
<td>Chart review of all active out-patients.</td>
<td>1 d in 2002</td>
<td>1–18</td>
<td>1292</td>
<td>N. R.</td>
<td>N. R.</td>
<td>N. R.</td>
</tr>
<tr>
<td>Reed et al. (2003)</td>
<td>Australia</td>
<td>Out-patients. One CAMHS.</td>
<td>Audit of all active cases.</td>
<td>1 Dec 1999.</td>
<td>3–18</td>
<td>734</td>
<td>5.5%</td>
<td>N. R.</td>
<td>18.3% SSRIs: 8.4%</td>
</tr>
<tr>
<td>Sourander et al. (2004)</td>
<td>Finland</td>
<td>In-patients. National study.</td>
<td>Questionnaires about all in-patients in Finland.</td>
<td>1 d in January 2000.</td>
<td>≤18</td>
<td>475</td>
<td>17.2%</td>
<td>N. R.</td>
<td>47.3% (SSRIs)</td>
</tr>
</tbody>
</table>

AD, Antidepressant; ADHD, attention deficit hyperactivity disorder; Anticonv, anticonvulsant; AP, antipsychotic; BZD, benzodiazepine; CAMHS, Child and Adolescent Mental Health Service (UK and Australia); MS, mood stabilizer (including lithium and anticonvulsants); COMB, combination; KiGGS, National German Health Interview and Examination Survey for Children and Adolescents; N. R., not reported; SCHIP, State Children’s Health Insurance Program (USA); SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; Stim, stimulant; TCA, tricyclic antidepressant.

* Most frequent combination in the study.
† In some studies reporting prescription trends, only the most recent data are included.
Table 2. Randomized controlled trials, open trials, naturalistic studies, chart reviews and case series assessing the use of polypharmacy with antidepressants in children and adolescents

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study</th>
<th>Combination</th>
<th>Study</th>
<th>n</th>
<th>Age (yr)</th>
<th>Method</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>Strober et al. (1992)</td>
<td>Li + imipramine</td>
<td>Open trial 3 wk</td>
<td>24</td>
<td>Mean: 15.4</td>
<td>Addition of Li to non-responders after 6 wk open-label imipramine. Results were compared with a naturalistic cohort treated with imipramine in monotherapy.</td>
<td>HAMD decreased in COMB (18.3 ± 5.7 to 13.4 ± 4.8, p &lt; 0.001) and in imipramine monotherapy (18.5 ± 6.1 to 15.4 ± 5.1, p &lt; 0.001). COMB vs. monotherapy: n.s. Improvement in HAMD: COMB: 26 ± 13 % vs. imipramine: 16 ± 7 % (p &lt; 0.05).</td>
<td>No discontinuations due to AEs. Most frequent AEs for the COMB were polyuria and tremor (7/24).</td>
</tr>
<tr>
<td>Treatment-resistant MDD</td>
<td>Ryan et al. (1988)</td>
<td>Li + TCA</td>
<td>Chart review</td>
<td>14</td>
<td>14–19 Mean: 16.9</td>
<td>Addition of Li to non- or partial responders after adequate trial with TCA for at least 4 wk</td>
<td>In week 6, significant decrease in global CGI: 4.0 ± 1.6 to 3.3 ± 1.0 (p &lt; 0.007). 6/14 responders (response defined as CGI-I ≤ 2 and CGI-S ≤ 2).</td>
<td>No withdrawals due to AEs. 13/14 patients reported AEs. COMB: 8/14 tremor (4/14 in monotherapy), dizziness 5/14 (10/14), nausea 4/14 (2/14), dry mouth 5/14 (0/14), polydipsia/polyuria 3/14 (0/14), blurred vision 3/14 (0/14). Other AEs did not show increased frequency with the COMB. 5/10 reported no AEs. 4/10 sedation. 1/10 intolerable sedation 8/10 gained weight. Mean weight gain: 2 ± 3.3 kg. No serious AEs.</td>
</tr>
<tr>
<td>Treatment-resistant MDD</td>
<td>Pathak et al. (2005)</td>
<td>SSRI + Quetiapine</td>
<td>Case series</td>
<td>10</td>
<td>13–18 Mean: 15.7</td>
<td>Insufficient response to previous treatment with SSRIs for 8 wk. Response to treatment defined as (CGI-I ≥ 2). AEs defined as any unwanted health changes identified after addition of quetiapine or medical symptoms that increased in severity.</td>
<td>7/10 (70%) responded to COMB treatment. Positive effect on self-harming behaviour in 3/10.</td>
<td></td>
</tr>
<tr>
<td>MDD and high risk for bipolarity</td>
<td>Findling et al. (2008)</td>
<td>Paroxetine + DIV</td>
<td>RCT. Mean follow-up 22 wk</td>
<td>9</td>
<td>7–16 Mean: 11.8</td>
<td>Offspring of parents with BPD with MDD (CDRS-R ≥ 40 and CGI ≥ 4). Randomized to either paroxetine or paroxetine + DIV. Efficacy: YMRS, CDRS-R, C-GAS, CGI-S and CGI-I. Only CDRS-R values are reported in the article.</td>
<td>CDRS-R mean scores, baseline/end of study: Paroxetine: 52/29, COMB: 46/32. Comparable temporary relief of depressive symptoms in both groups, but neither treatment long-term efficacy nor protective capacity: 5/9 patients hypomanic/ manic symptoms or suicidality and study was discontinued.</td>
<td>Monotherapy: most frequent AEs: gastrointestinal. 1/4 hypomanic symptoms, 1/4 suicide attempt, 1/4 suicide threat. All of them discontinued the study. COMB: 2/5 drowsiness, 2/5 sedation, 1/4 tremor, 1/4 manic symptomatology. 1/5 patients in COMB discontinued treatment due to AEs (sedation). COMB poorer tolerance than paroxetine and more frequent sedation.</td>
</tr>
</tbody>
</table>
### Table 2 (cont.)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study</th>
<th>Combination</th>
<th>Study</th>
<th>n</th>
<th>Age (yr)</th>
<th>Method</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
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<tbody>
<tr>
<td>MDD with comorbid attentional disorders</td>
<td>Findling (1996)</td>
<td>SSRI (fluoxetine or sertraline) + Stimulant (MPH or DMP)</td>
<td>Case-series. Open-label. Mean follow-up 7.6 months</td>
<td>7†</td>
<td>10–16</td>
<td>Mean: 13.9</td>
<td>MDD had already responded to SSRI. Stimulants were added. Qualitative measures of efficacy and safety.</td>
<td>Improvement in residual ADHD symptoms in all patients. 3/7 complete remission, 3/7 marked improvement, 1/7 moderate improvement. No significant increases in BP or pulse, manic symptoms, aggressiveness or suicidality. No specific AEs that could be attributable to the COMB.</td>
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<tr>
<td>Anxiety disorders</td>
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<tr>
<td>Treatment-resistant OCD</td>
<td>Masi et al. (2009)</td>
<td>SRI (SSRI or clomipramine) + SGAs</td>
<td>Naturalistic retrospective. Follow-up ≥ 6 months</td>
<td>43*</td>
<td>6–18</td>
<td>Mean: 14.5</td>
<td>Part of a naturalistic study in 220 OCD patients. 85/220 (38.6 %) received SGAs + SRI (43/85 (50.6 %) as augmenting strategy, 42/85 (49.9 %) for co-morbidity). Response: CGI-I ≤ 2 and a CGI-S ≤ 3 in 3 consecutive months.</td>
<td>25/43 (58.1 %) of those receiving SGAs as augmenting strategy responded. Not reported</td>
</tr>
<tr>
<td>Treatment-resistant OCD</td>
<td>Masi et al. (2010)</td>
<td>SRI (SSRIs or clomipramine) + aripiprazole</td>
<td>Open-label. Follow-up 6 months</td>
<td>39</td>
<td>12–18</td>
<td>Mean: 14.6</td>
<td>Patients had failed in 2 previous SRI trials. Concomitant treatments allowed (MS and MPH). Response: CGI-I ≤ 2, CGI-S ≤ 3 and C-GAS ≥ 50 in 3 consecutive months. No information on how AEs were assessed.</td>
<td>27/39 (59 %) responded. 10/16 (62.5 %) of those with tics/Tourette. CGI-S decreased from 6.5 ± 0.9 to 3.5 ± 1.0, p &lt; 0.0001. C-GAS increased from 39.2 ± 5.8 to 49.8 ± 9.0, p &lt; 0.0001. No discontinuations due to AEs. 4/39 (10.3 %) mild transitory agitation 4/39 (10.3 %) mild sedation 3/39 (7.7 %) sleep disorders 3/39 (7.7 %) weight gain ≥ 2 kg but &lt; 5 kg.</td>
</tr>
<tr>
<td>Treatment-resistant OCD</td>
<td>Thomsen (2004)</td>
<td>SSRI + Risperidone</td>
<td>Open-label 12 wk</td>
<td>17</td>
<td>15–18</td>
<td>Mean: 16.6</td>
<td>OCD symptoms remained after 2 SRI monotherapy trials + CBT. Efficacy: Y-BOCS, C-GAS. Safety: Systematic for tiredness, sleep problems, agitation and irritability. Weight control.</td>
<td>Y-BOCS/CY-BOCS decreased (19.9 ± 2.9 vs. 24.2 ± 2.6 at baseline, p &lt; 0.001), C-GAS increased (74.7 ± 9.6 vs. 69.4 ± 11.4 p &lt; 0.001). 1/17 patients dropped to subclinical OCD level (Y-BOCS &lt; 15). 4/17 patients moderate improvement (25 % reduction in Y-BOCS). 0/17 worsening of OCD symptoms. Weight gain (defined as increase ≥10 %) in 7/17 (41.2 %). Mean change in weight since addition of risperidone 2.7 % (0–10.3 %), 5.3 kg (0–24 kg). Mean BMI increased from 20.9 to 22.5. After combined treatment: 3/17 BMI ≥ 25 (overweight). Sedation in 4/17 (23.5 %).</td>
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<tr>
<td>Treatment-resistant OCD and/or with comorbidity</td>
<td>Fitzgerald et al. (1999)</td>
<td>SRI (SSRI or clomipramine) + Risperidone</td>
<td>Case series</td>
<td>4</td>
<td>8–13</td>
<td>Mean: 10.25</td>
<td>Partial response or intolerance to SRI in monotherapy. 2/4 cases comorbidity with tics/Tourette, 3/4 aggraveness or irritability/activation with SSRIs. Assessments using traditional clinical observation.</td>
<td>Clinical improvement (in residual OCD symptoms, tics or irritability/aggressiveness) in all patients, maintained for at least 4–8 months. Only one patient quantitative measures of efficacy (Y-BOCS decreased from 33 before start of SRI to 17). 1/4 weight gain (7.7 kg). 2/4 sedation.</td>
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</table>
### Treatment resistant OCD

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<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Study Design</th>
<th>Duration</th>
<th>Mean Age</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Figueroa et al. (1998)</td>
<td>Clomipramine + SSRI</td>
<td>Case series</td>
<td>Open-label</td>
<td>6-9 months</td>
<td>15.7</td>
<td>Addition of SSRI or clomipramine to patients with insufficient response to either drug. 4/6 comorbid depressive or anxiety disorder. Assessments using traditional clinical observation. No quantitative assessments of efficacy. Combined treatment was effective in the long-term for OCD and depressive symptoms in all patients (6/6), both with (2/6) or without (4/6) comorbid anxiety or depression.</td>
</tr>
<tr>
<td>Simeon et al. (1990)</td>
<td>Clomipramine + fluoxetine</td>
<td>Case series</td>
<td>Open-label</td>
<td>4-28 weeks, Follow-up 8-44 weeks</td>
<td>14.2</td>
<td>OCD previously treated with clomipramine with insufficient efficacy or intolerable side effects. 5/6 comorbid with depressive/anxiety disorders. Efficacy: CGI-I. Improvement in all patients (5/6) marked clinical global improvement, 1/6 moderate clinical global improvement.</td>
</tr>
<tr>
<td>Thomsen and Mikkelsen (1999)</td>
<td>SSRI + buspirone</td>
<td>Case series</td>
<td>Open-label</td>
<td>6-15 weeks</td>
<td>16.7</td>
<td>OCD with insufficient response to SSRIs + CBT Efficacy: Y-BOCS. Safety assessed by patient reports on AE. 3/6 mild complaints: 3/6 hand tremors, 1/6 weight loss, 1/6 awakening with bad dreams. COMB better tolerated and fewer AEs than clomipramine alone. No discontinuations due to AEs. 5/6 reported no AE. 2/6 sedation. 1/6 extreme somnolence.</td>
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</table>

### Other disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Study Design</th>
<th>Duration</th>
<th>Mean Age</th>
<th>Outcomes</th>
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<tr>
<td>Kratochvil et al. (2005)</td>
<td>Atomoxetine + fluoxetine</td>
<td>Atomoxetine + placebo</td>
<td>RCT 5 weeks</td>
<td>173</td>
<td>11.3</td>
<td>Atomoxetine added to both arms after 3 wk on fluoxetine or PBO. Efficacy: ADHDRS IV, CDI, CDRS-R, MASC and CGI-S. Safety: Open-ended questions, vital signs and lab tests. In both groups significant (p&lt;0.001) decreases in ADHDRS (COMB - 24.0 ± 13.6 vs. -20.5 ± 12.9 with monotherapy; COMB vs. monotherapy n.s. (p=0.121), CDI (COMB - 8.8 ± 8.1 vs. -5.4 ± 10 with monotherapy, p=0.04), CDRS-R (COMB - 20.4 ± 13.6 vs. monotherapy -17.6 ± 11.8, n.s. (p=0.342) and MASC (13.4 ± 16.0 vs. -11.3 ± 19.0. n.s. (p=0.489). CGI-S increased in both groups (p&lt;0.001): COMB 2.3 ± 1.4 vs. monotherapy 1.9 ± 1.3, n.s. p=0.06. Low withdrawal rates due to AEs (COMB 3/115 vs. 1/46 in atomoxetine + PBO, n.s.). COMB: Greater weight loss (1 kg vs. -0.4 kg in PBO, p&lt;0.01), greater increases in BP or pulse, p&lt;0.05 (n.s. differences in clinically significant increases in BP or pulse), trend towards greater appetite decrease in COMB group (p=0.055). n.s. differences in manic, activation, suicidal or aggressive symptoms.</td>
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<tr>
<td>Diagnosis</td>
<td>Study</td>
<td>Combination</td>
<td>Study</td>
<td>n</td>
<td>Age (yr)</td>
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<tr>
<td>ADHD with comorbid anxiety disorder</td>
<td>Abikoff et al. (2005)</td>
<td>Stimulant + fluvoxamine</td>
<td>RCT 8 wk.</td>
<td>25</td>
<td>6–17</td>
<td>Mean: 10.6</td>
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<tr>
<td></td>
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<td>Stimulant + placebo</td>
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<tr>
<td>ADHD with insufficient response to stimulants</td>
<td>Gammon and Brown (1993)</td>
<td>MPH + fluoxetine</td>
<td>Open-label 8 wk.</td>
<td>32</td>
<td>9–17</td>
<td>Mean: 13.8</td>
</tr>
<tr>
<td>ASD</td>
<td>Anagnostou et al. (2006)</td>
<td>SSRI + DIV</td>
<td>RCT 8 wk.</td>
<td>6</td>
<td>6</td>
<td>Mean: 9.5</td>
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Prader-Willi Syndrome

Smathers et al. (2003)

Topiramate + SSRI Open-label Follow-up to 1 yr 5* 11–19 Mean: 13.6 Topiramate was added to previous treatment for compulsive eating in 8 patients. 5/8 patients were already on SSRI.

Efficacy: Mood and behaviour by parental questionnaires and phone surveys (mood, compulsive eating, skin picking, general overall behaviour), weight. No information on AEs assessment.

After topiramate addition, 4/5 patients improved in compulsive eating, violent behaviour and mood. Of patients remaining in treatment, 3/4 lost weight, 1/4 reduction in weight gain.

Sedation (separate rates for patients on the COMB SSRI + topiramate not provided).

Tourette’s syndrome with co-morbidity

Hawkridge et al. (1996)

SRI + neuroleptic Chart review 5†† Mean: 15.4†† 4/5 patients co-morbidity with OCD (other: ADHD, MDD, conduct disorder, GAD). Improvement of OCD symptoms in patients with co-morbid Tourette and OCD (4/5) and of tics in 2/5.

4/5 no significant AEs. 1/5 urinary retention.

ADHD, attention deficit hyperactivity disorder; ADHD-RS, Attention Deficit Hyperactivity Disorder Rating Scale; AE, adverse event; ASD, autism spectrum disorder; BD, bipolar disorder; BP, blood pressure; CBT, cognitive-behavioural therapy; CDI, Children’s Depression Inventory; C-GAS, Children’s Global Assessment Scale; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression Severity; CGI-I, Clinical Global Impression Improvement; COMB, combination; CPRS, Conners Parents Rating Scale; CRDS-R, Children’s Depression Rating Scale Revised; DIV, divalproex; DMA, dextroamphetamine; GAD, generalized anxiety disorder; MPH, methylphenidate; MASC, Multidimensional Anxiety Scale for Children; MDD, major depressive disorder; MS, mood stabilizer; n.s., not significant; OCD, obsessive-compulsive disorder; PARS, Paediatric Anxiety Rating Scale; PBO, placebo; RCT, randomized controlled trial; SGA, second-generation antipsychotic; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; YMRS, Young Mania Rating Scale; YBOCS, Yale–Brown Obsessive-Compulsive Scale.

* n refers to the number of patients receiving the study combination.
† In articles including both adult and paediatric patients, n refers to patients aged 0–19 yr.
†† In naturalistic studies, open trials and chart reviews, mean age refers to the group taking the study combination. In RCTs mean age refers to the whole group.
††Age range not provided, mean age: 15.4 ± 5.7 yr. Authors refer to their ‘predominantly paediatric clinic’ but do not inform on how many patients were aged > 19 yr.
beneficial effect of the addition of lithium to TCAs (Ryan et al. 1988; Strober et al. 1992) or venlafaxine (Walter et al. 1998) for the management of treatment-resistant depression.

Treatment-resistant OCD

One naturalistic study, one open trial and two case series assessed the efficacy of the combination of SSRIs or clomipramine with SGAs for treatment-refractory OCD (Fitzgerald et al. 1999; Thomsen, 2004; Masi et al. 2009, 2010). They all suggested the combination to be effective, with >60% of patients showing improvement while on the combination. Two other small open studies assessed the combination of clomipramine and SSRIs for treatment-resistant OCD. These studies suggested the combination to be useful (Simeon et al. 1990; Figueroa et al. 1998) but potentially related to increased rates of adverse events (AEs), which were mainly cardiovascular, i.e. tachycardia and QTc prolongation (Figueroa et al. 1998). Buspirone augmentation of SSRIs was also associated with marked improvement in three patients out of a six-case series of treatment-resistant OCD (Thomsen and Mikkelsen, 1999).

Co-morbidity between ADHD and anxiety and/or depressive disorders

One 5-wk RCT did not find the combination of fluoxetine with atomoxetine to be more efficacious than atomoxetine alone in patients with co-morbid ADHD and depressive or anxiety disorders, with only a slight advantage for depressive symptoms in the combination group (Kratochvil et al. 2005). Similarly, another placebo-controlled RCT did not find that the addition of fluoxetine to methylphenidate in 25 patients with ADHD and co-morbid anxiety disorder, who presented with persistent anxiety symptoms after improvement of ADHD, provided any advantage for the treatment of residual anxiety symptoms (Abikoff et al. 2005).

Conversely, one open-label study performed in seven patients with co-morbid MDD and ADHD in whom depression had already responded to SSRIs did find that the addition of a stimulant improved residual ADHD symptoms (Findling, 1996), whereas another open-label study reported the potential efficacy of fluoxetine as an augmenting strategy for treatment of ADHD with insufficient response to stimulants in 32 patients, most of whom presented with co-morbid depressive or anxiety disorders (Gammon and Brown, 1993).

Other diagnoses

Four small studies assessed combination patterns for the treatment of Prader–Willi syndrome, autism spectrum disorder, MDD and high-risk of bipolarity and Tourette’s syndrome with co-morbidity (see Table 2).

Safety

Data from the few open-label and controlled studies about combining antidepressants with other drug classes did not generally find increases in relevant AEs. Combining SSRIs with stimulants was generally well tolerated, but some case reports related it to an increased risk of seizures and myoclonus in paediatric patients (Feeley and Klykylo, 1997; Ghaziuddin et al. 2001; Schertz and Steinberg, 2008). A risk of seizures was also reported for the combination of bupropion and stimulants (Ickowicz, 2002). As for SSRIs combined with antipsychotics, sedation and weight gain were reportedly the most common AEs in open studies and case series, whereas case reports related the combination to the occurrence of enuresis (Touk and Buck, 1996), extrapyramidal symptomatology and tardive dyskinesia (Budman et al. 1995; Daniel et al. 1996). In the case of anticonvulsants, sedation also seems to be frequently related to their combination with SSRIs (see Table 2).

Discussion

Increase in the use of polypharmacy involving antidepressants

Although different methodologies, with higher sensitivity of more recent studies, may have influenced the results, prescribing trend studies suggest an increase in the use of polypharmacy involving antidepressants in recent years (Rushton and Whitmire, 2001; Comer et al. 2010). This increase has been reported across countries, with higher rates usually reported for the USA than for most non-US countries (Zito et al. 2008). Factors related to the setting, type of health insurance, socio-demographic features, co-morbidities and severity of the disorders, as well as cultural attitudes, influence rates of psychotropic polypharmacy in children and adolescents (Martin et al. 2003; Safer et al. 2003; dosReis et al. 2005; Staller et al. 2005; Duffy et al. 2005; Dean et al. 2006; Russell et al. 2006; Fontanella et al. 2009). These factors may also influence rates of polypharmacy in patients with paediatric MDD, which seems to be more common in non-African American male patients and patients with co-morbidities (McIntyre and Jerrell, 2009). Although specific data on correlates of polypharmacy with antidepressants are lacking, it can be posited that many of these factors also affect this practice.

One reason for this recent increase could be the growing interest in the diagnosis and management of paediatric mood and behavioural disorders. Thus, the numbers of children and adolescents diagnosed and treated for MDD (Ma et al. 2005; Skaer et al. 2009), ADHD (Robison et al. 2002; Olsson et al. 2003b) and paediatric BD (Blader and Carlson, 2007; Moreno et al. 2007) have increased substantially in the last few decades, whereas the number of pharmacological studies performed in paediatric patients remains low as compared with adults (American...
Academy of Children and Adolescent Psychiatry, 2009). This fact may be related to the well-known difficulties of conducting clinical trials in paediatric patients (Caldwell et al. 2004) and means that clinical choices must often be based on inadequate information or results from adult studies, even if there seems to be a failure to publish negative findings and risks might be underestimated (Safer et al. 2003). Moreover, the impression that current antidepressants are potentially related to fewer side effects can make prescribers take the risk of trying new combinations with less concern for safety, whereas other clinicians might feel hesitant to modify multiple drug patterns that were introduced by other professionals or that seemed to be effective at the beginning (Safer et al. 2003). Other factors involved in this increase would be current diagnostic systems such as the DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 1992) that foster diagnosis of co-morbid conditions (Rittmannsberger, 2002). For example, high reported rates of co-morbidity between ADHD and BD in some studies could be the result of overlapping symptoms and diagnostic criteria leading to misdiagnosis of BD or excessive diagnosis of co-morbidities and should call into question the need for polypharmacy in many of those cases. Greater specialization of practitioners in pharmacotherapy, with less interest in non-pharmacological approaches, as well as pressure for rapid symptom improvement and cost considerations, which tend to be more prominent in health care systems with more private insurance plans (Vitiello, 2008), probably also favour an increase in co-prescription of medication.

Furthermore, the use of polypharmacy with antidepressants is also prompted by clinical factors such as the severity of paediatric mood and anxiety disorders and frequent co-morbidity with other psychiatric and medical conditions (Masi et al. 2007; Essau, 2008; Esbjorn et al. 2010; Kurtz and Abrams, 2010; de Wit and Snoek, 2011). The fact that many paediatric patients with depression or OCD fail to achieve remission and present with residual symptoms after treatment with antidepressants as monotherapy (POTS Team, 2004; Kennard et al. 2006; Bridge et al. 2007; Storch et al. 2008) could also prompt clinicians to use polypharmacy strategies in these populations.

**Evidence supporting the use of polypharmacy regimes involving antidepressants: relationship with current clinical guidelines and practice parameters**

As expected, there was little evidence supporting the use of polypharmacy regimes involving antidepressants and most of the information was provided by case series, open studies with small samples, a few RCTs and anecdotal or secondary evidence from studies designed for other purposes. Although also lacking, there is more evidence, based on controlled studies, supporting the use of combination therapies with antidepressants in adults (Bloch et al. 2006; Wijkstra et al. 2006; DeBattista and Hawkins, 2009; Vieta et al. 2010). In paediatric patients, augmentation of antidepressants with SGAs in refractory OCD, and treatment of ADHD and co-morbid anxiety or depressive disorders were the most studied options.

In spite of the lack of RCTs and the small samples, the limited current evidence supports augmentation of SSRIs with SGAs in treatment-resistant paediatric OCD (Fitzgerald et al. 1999; Thomsen, 2004; Masi et al. 2009, 2010), in line with clinical guideline recommendations (American Academy of Children and Adolescent Psychiatry, 1998; National Institute for Health and Clinical Excellence, 2005b). There is also some evidence for the use of clomipramine as augmentation strategy for SSRIs in this population (Simeon et al. 1990; Figueroa et al. 1998), although the potential risk of cardiovascular AEs calls for close monitoring of patients on the combination (Figueroa et al. 1998).

Surprisingly, very little information was found on the use of polypharmacy involving SSRIs for the treatment of paediatric depression. Only two small case series supported the concomitant use of SGAs and SSRIs for the management of residual symptoms or treatment-resistant depression (Pathak et al. 2005; Good, 2006). To date, most clinical guidelines do not recommend augmentation of SSRIs with SGAs for paediatric patients with treatment-resistant depression and, in light of the lack of sufficient empirical data, does not seem to be justified, mainly considering potential safety concerns associated with long-term treatment with SGAs (Fraguas et al. 2011). We were unable to find any studies assessing the combined use of two antidepressant classes for the treatment of paediatric depression. Although a possible alternative for treatment-resistant cases, it should be noted that one recent adult study has questioned the efficacy of this practice, while highlighting the increased frequency of AEs (Rush et al. 2011).

Other combinations recommended by paediatric clinical guidelines (Birmaher et al. 2007; Hughes et al. 2007), such as augmentation of SSRIs with lithium in treatment-resistant depression or concomitant use of antipsychotics and antidepressants for the treatment of psychotic depression, have been under-studied in paediatric populations. Although lithium has been claimed to be an adequate augmentation strategy for treatment-resistant MDD in adults (Crossley and Bauer, 2007) and considered useful for paediatric treatment-resistant depression in clinical guidelines (Birmaher et al. 2007; Hughes et al. 2007), to our knowledge only three studies have assessed the efficacy of lithium augmentation of TCAs (Ryan et al. 1988; Strober et al. 1992) or venlafaxine (Walter et al. 1998) and no studies have specifically assessed augmentation strategies of SSRIs. All studies detected a beneficial effect of the addition of lithium. However, the fact cannot be overlooked that those studies assessed the addition of lithium to antidepressant classes that have not proved to be efficacious per se for the...
treatment of paediatric depression (Moreno et al. 2006) and potential AEs of lithium in these populations may limit its application (Lopez-Larson and Frazier, 2006).

In the case of ADHD with co-morbid anxiety and depressive disorders, current clinical guidelines recommend treating the disorder that causes the most impairment first and then adding medication for the co-morbid diagnosis in case residual symptoms persist (Pliszka et al. 2006). One open-label study in patients whose depression had responded to SSRIs found that the addition of stimulants improved residual attention symptoms (Findling, 1996). However, in one RCT the addition of SSRIs to methylphenidate was comparable to methylphenidate alone in patients with ADHD plus anxiety disorders, with residual anxiety symptoms after response of ADHD symptoms (Abikoff et al. 2005). Another RCT did not find clinically significant differences between atomoxetine alone and in combination with fluoxetine in patients with co-morbid ADHD and anxiety and depressive disorders, both being equally efficacious strategies (Kratchovili et al. 2005).

Although some drugs could be useful as monotherapy for the treatment of co-morbid ADHD and depressive or anxiety disorders (Daviss et al. 2001; Geller et al. 2007), high prevalence and severity of co-morbidity between the two disorders often call for the use of additional strategies (Larson et al. 2011). However, it remains unclear whether the combination of stimulants and antidepressants is the optimal strategy for these situations and which particular drugs it is preferable to include in polypharmacy patterns.

**Potential risks associated with polypharmacy with antidepressants**

Safety data on polypharmacy with antidepressants were also limited. Most combinations were relatively well tolerated in open-label studies and RCTs, but there were several case reports of severe AEs in paediatric patients treated with combinations involving antidepressants (Budman et al. 1995; Burke et al. 1995; Cruz-Flores et al. 1995; Daniel et al. 1996; Took and Buck, 1996; Feeney and Klykylo, 1997; Sailee et al. 2000; Ghaziuddin et al. 2001; Ickowicz, 2002; George et al. 2005; Coskun and Zoroglu, 2008; Schertz and Steinberg, 2008; Park and Jung, 2010; Mahapatra et al. 2011). These severe AEs were mainly related to unexpected or underestimated pharmokinetic interactions, potentiation of hyperserotonergic states or poorly understood pharmacodynamic mechanisms due to neurodevelopmental status or genetic vulnerability.

The combination of stimulants and antidepressants was reported to be generally well tolerated, with low rates of significant AEs, low withdrawal rates due to AEs and AE rates similar to stimulants in monotherapy. Decreased appetite, weight loss and greater increases in blood pressure and pulse (generally clinically non-significant) seemed to be more frequent in patients on polypharmacy. However, risk of seizures and myoclonus was reported in some individual case reports and should be considered when managing the combination (Feeney and Klykylo, 1997; Ghaziuddin et al. 2001; Ickowicz, 2002; Schertz and Steinberg, 2008). This is consistent with previous data regarding these drug classes (Graham and Coghill, 2008; Jerrell and McIntyre 2009; Settle 1998; Wilens et al. 2004) and might be related to the pharmokinetic and pharmacodynamic properties of the compounds, which may increase the efficacy but also the risks of the combination (Belle et al. 2002; Baird, 2003; Martin, 2003).

With regard to the combination of SSRIs with clomipramine, safety data were discordant, with one study reporting better tolerance for the combination than for clomipramine alone and the other one reporting high rates of AEs for the combination (Simeon et al. 1990; Figueroa et al. 1998), probably due to the differences in dosing patterns. In any case, attention should be paid to potential cardiovascular AEs with the combination (Figueroa et al. 1998; National Institute for Health and Clinical Excellence, 2005b). As for the concomitant use of SSRIs and antipsychotics, somnolence and weight gain seemed to be frequent with the combination. That was also the case for the combination with anticonvulsants, where sedation was found to be more frequent in patients on polypharmacy. However, it must be noted that most of these studies were of short duration, thus preventing the detection of some relevant long-term risks of the combination of SSRIs with SGAs and MSs such as metabolic AEs (Moreno et al. 2010).

Naturalistic follow-up data from adults suggest that the combination of antidepressants and SGAs might be related to problematic weight-gain and metabolic AEs in the long-term (Andersen et al. 2005; APA, 2006). In paediatric patients, SSRIs, anticonvulsants and SGAs have been independently associated with long-term weight gain and/or increased metabolic risk (Correll and Carlson, 2006; Fraguas et al. 2010, 2011; Jerrell and McIntyre, 2010), which calls for appropriate monitoring of weight and metabolic disturbances in patients on polypharmacy with both drug classes. Other relevant long-term AEs of SGA treatment such as the development of tardive dyskinesia or hormonal disturbances should be also monitored in this sensitive population (Fraguas et al. 2011). On the other hand, a small case series has related SSRIs to reduction in growth speed, which should be considered when given concomitantly with stimulants (Weintrob et al. 2002; Faraone et al. 2008).

Furthermore, other potential risks of SSRIs should be also taken into account when managing polypharmacy. For example, behavioural activation related to SSRIs (Kastelic et al. 2000; Safer and Zito, 2006) can be increased if they are combined with other substances with activating properties. However, only one of the studies assessing the combination of SSRIs with stimulants reported increased activation leading to discontinuation of
treatment in one patient (Gammon and Brown, 1993) and none of them reported manic symptomatology. The risk of SSRI-induced activation and manic switch may also prompt *per se* the necessity of polypharmacy regimes (Anagnostou et al. 2006), especially in depressed children and adolescents with BD or at high risk of bipolarity, in whom antidepressants, although useful for the treatment of depressive symptoms, seem to be related to a higher risk of manic relapse (Biederman et al. 2000), making it advisable to add concomitant MIs (Kowatch et al. 2005). However, it should be noted that an RCT performed in young people with MDD and at high risk of bipolarity comparing the combination of divalproex and paroxetine vs. paroxetine alone found manic/hypomanic symptoms and suicide risk to be very common in both groups (Findling et al. 2008).

**Clinical management of patients with multiple psychotropic medication regimes involving antidepressants**

A careful therapeutic and monitoring plan should be implemented when managing polypharmacy with antidepressants in clinical settings. Patients and their relatives should be informed about the potential risks of the combination and about alarming symptoms. Furthermore, clinicians should be aware of the available evidence supporting certain combinations and treat any side effects, when possible, by reducing doses rather than by adding new drugs. Complex medication regimes should be reviewed regularly, considering the possibility of withdrawing medications that are ineffective or no longer necessary. In this situation, it is advisable to remove first the medication that was added as an augmenting strategy or for the treatment of residual symptoms, following the principle of maintaining the drug with the greatest prophylactic efficacy for the long-term. In case of co-morbidity, it is recommended to initially withdraw the medication for the disorder that is more likely to respond to acute treatment or that is less impairing (Rittmannsberger, 2002; Safer et al. 2003; American Academy of Children and Adolescent Psychiatry, 2009).

**Further lines of research**

Polypharmacy with antidepressants remains an understudied phenomenon despite its frequency and clinical relevance. This is related not only to the fact that clinical trials can assess only a limited number of combinations, but also because they are not likely to include more complicated patients (i.e. those having co-morbidity, more severe symptomatology or suicide risk) with the result that current research usually evaluates the efficacy of interventions, but it is not able to provide useful information on their effectiveness in real-life patients. This situation is even more marked in the case of paediatric mood and anxiety disorders, where research has greater regulatory and practical limitations, whereas co-morbidity and severity play a very relevant role in the typical clinical picture of the disorder. A need exists for naturalistic long-term studies including a sufficient number of patients reflecting the actual clinical features of paediatric mood and anxiety disorders, in order to acquire applicable information on the efficacy and safety of the most frequently needed polypharmacy patterns involving antidepressants. On the other hand, further studies on the pharmacokinetics and pharmacodynamics of antidepressants in paediatric patients, as well as on the neurodevelopmental effects of chronic exposure to such substances before adulthood should be implemented in order to improve knowledge of the neurobiological support for polypharmacy with antidepressants and its associated risks. Finally, research on epidemiological factors would benefit from more homogeneous definitions of polypharmacy, time-frames and methodological approaches, favouring studies providing information on clinical and diagnostic aspects that may shed greater light on the phenomenon.

**Limitations and implications**

Our review was limited by the difficulties of performing the literature search, given the heterogeneity of terms and articles that could include information relevant for the review and the risk of missing relevant data. Furthermore, methodology, study populations and definition of polypharmacy differed markedly among studies, thus making it difficult to establish comparisons and to draw definite conclusions. Nevertheless, this review is, to our knowledge, the first to specifically address this understudied phenomenon and provide a general overview of the extent of use of polypharmacy with antidepressants in paediatric patients, highlighting its increasing prevalence and its relationship with actual clinical necessities. This clearly contrasts with the scant empirical evidence to support its use and knowledge about its potential risks, thus raising clinical and research questions to be answered in the future.

**Conclusions**

There has been a recent increase in polypharmacy involving antidepressants in children and adolescents. Although SSRIs are efficacious for treating acute depression and anxiety in a significant percentage of paediatric patients, many of them continue presenting residual symptoms after adequate treatment trials, which calls for additional therapeutic strategies such as combined treatments. Despite the scarcity and methodological limitations of specific studies, preliminary evidence highlights the potential clinical utility of certain combination patterns involving antidepressants. Given that polypharmacy with antidepressants has become a strategy for the management of some severely ill paediatric...
patients, as acknowledged by clinical guidelines, further empirical research studies on this issue should be urgently developed.

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Statement of Interest

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References


Cossik M, Zoroglu S (2008). Tactile and visual hallucinations in schizophrenia patients, as acknowledged by clinical guidelines, further empirical research studies on this issue should be urgently developed.


