



Research Article

SIDE EFFECTS OF MEDICATIONS USED TO TREAT ADHD IN BRAZIL'S PUBLIC HEALTH

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ABSTRACT

To diagnose Attention Deficit Hyperactive Disorder (ADHD) accurately and treat it effectively requires a multidisciplinary, multimodal approach that involves psychosocial and psychopharmacological interventions. Characteristics that one may be observed in persons with ADHD include excessive movement of extremities and inability to sit still for extended periods of time, aggressive behavior and sudden mood swings, and carelessness and absent mindedness that may manifest themselves as inattentiveness in class and contribute to impaired academic performance. There is a significantly higher prevalence of ADHD in boys, who are 1.5 to 5.8 times more likely than girls to be diagnosed. The disorder often has a chronic course with about 70% of affected children presenting threshold symptoms and associated impairments in adolescence and 30 to 50% presenting them in adulthood. To address such concerns and determine the biosafety of such medications, the present study comprises an assessment of the side effects of medications provided by Brazil's public health service to treat ADHD.

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INTRODUCTION

Attention deficit-hyperactivity disorder (ADHD) is a common neuropsychiatric disorder with preschool-age onset. Thought to affect 3 to 5% of all school-age children (Rohde *et al*, 1999) (Vasconcelos *et al*, 2003). It is characterized by easily recognizable symptoms of age-inappropriate hyperactivity, inattentiveness, and impulsivity (Rohde *et al*, 2004). ADHD is a global health problem, whose effects range from poor academic performance to psychosocial problems. To diagnose ADHD accurately and treat it effectively requires a multidisciplinary, multimodal approach that involves psychosocial and psychopharmacological interventions (Rhode *et al*, 1999) (Vasconcelos *et al*, 2003) Obstacles to successful diagnosis and treatment include the prevalence of myths about the disorder (Rohde, 2004).

Characteristics that one may be observed in persons with ADHD include excessive movement of extremities and inability to sit still for extended periods of time, aggressive behavior and sudden mood swings, and carelessness and absent mindedness that may manifest themselves as inattentiveness in class and contribute to impaired academic performance (Knipp, 2006) (Sax, Kautz, 2003).

The current edition of the *Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5, 2013)* defines ADHD

according to two behavioral domains: inattentiveness and hyperactivity/impulsivity. Each comprises nine possible symptoms, with the presence of at least six required for diagnosis as ADHD. With six or more symptoms of inattention, the diagnosis is the predominantly inattentive type, and with six or more symptoms of hyperactivity-impulsivity, the predominantly hyperactive-impulsive type. With at least six symptoms in the areas of inattention and hyperactivity-impulsivity, the diagnosis is ADHD-combined or mixed (DSM-5, 2013) Eighty percent of children diagnosed with ADHD display symptoms in both domains, though among the overall ADHD population, the predominately inattentive type of is most common (Vasconcelos *et al*, 2003).

The diagnostic criteria for ADHD requires the following:

1. At least six of the following symptoms of inattention have frequently persisted for at least six months to a degree unsuitable for and inconsistent with developmental level:

(a) Failure to pay attention to details or making careless mistakes in school or other work, (b) Difficulty in sustaining attention in tasks or play activities, (c) perception of not listening when spoken to directly (d) failure to follow instructions and complete schoolwork or workplace duties not arising from failure to understand instructions or oppositional behavior, (e) difficulty in organizing tasks and activities (f) avoidance of, aversion to, or unwillingness to engage in tasks that require sustained mental effort, such as schoolwork or domestic chores, (g) losing things required for tasks or activities, such as toys, school assignments, pencils, books, or

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other materials, (h) facile distraction from external stimuli, and (i) forgetfulness in daily activities.

2. At least six of the following symptoms of hyperactivity/impulsivity have frequently persisted for at least six months to a degree unsuitable for and inconsistent with developmental level: hyperactivity (a) fidgeting with hands or feet or moving while seated, (b) leaving seat in classroom or other situations in which remaining seated is expected, (c) running about or climbing excessively in inappropriate situations or in adolescents or adults, subjective feelings of restlessness, (d) difficulty in playing or engaging in leisure activities quietly, (e) restlessness or, on occasion, acting as if driven by a motor, (f) verbosity, impulsivity: (g) often gives answers before questions have been completed (h) difficulty waiting for the appropriate moment to speak, and (i) interrupting or intruding on others, e.g., in conversations or games).^{6,7}

Additional *DSM-5* criteria stipulate that some inattention and hyperactivity/impulsivity symptoms occur before age seven. Symptoms must also occur in at least two places, e.g., home and school, and cause social, academic, or professional impairment. They should not occur solely during the course of an invasive or schizophrenic or other psychotic disorder or be caused by another primary mental disorder, such as mood, anxiety, or dissociative disorders. The definitive diagnosis depends on the reliability of parent/teacher reports and the experience of doctors and psychologists in interpreting the patient's stories and history (Sax, Kautz, 2003).

There is a significantly higher prevalence of ADHD in boys, who are 1.5 to 5.8 times more likely than girls to be diagnosed. The disorder often has a chronic course with about 70% of affected children presenting threshold ADHD symptoms and associated impairments in adolescence and 30 to 50% presenting them in adulthood (Rohde *et al*, 1999) (Vasconcelos *et al*, 2003).

The presence of comorbid disorders is the rule rather than the exception. Common comorbidities in children and adolescents include oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, tic disorders, motor coordination disorder, learning disabilities, and problems in reciprocal social interaction and communication analogous to those described in autism spectrum disorders. In adolescence and adulthood, comorbid risk-taking behaviors, substance abuse disorders, antisocial personality disorder, and borderline personality disorder are increasingly prevalent. Numerous problems are associated with ADHD, such as poor academic performance, dropping out of school, social isolation, and reduced occupational success (Rohde *et al*, 2004) (Poeta, Rosa Neto, 2004).

There is not a universal protocol for the treatment of ADHD, and, in general, each country determines its recommendations based on the literature (Hodgkings, Shaw, Hetchman, 2012). There is, however, a consensus for the necessity of a comprehensive, multi-modal treatment plan, developed collaboratively by the physician, therapists, psychologists, family, and school, that integrates psychoeducation, caregiver training, educational and behavioral intervention, and medication, among other factors, to create an optimal treatment environment.

The United States Food and Drug Administration (FDA) has approved the use of methylphenidate; mixed amphetamine salts, including the recently introduced prodrug, lisdexanfetamine, a selective reuptake inhibitor of norepinephrine (atomoxetine); and sympatholytic antiadrenergic agents, such as clonidine and guanfacine. Bupropion, which inhibits reuptake of dopamine and norepinephrine, and tricyclic antidepressants, including imipramine, are listed in U.S. guidelines as medication options for ADHD (Pliszka *et al*, 2006) but are not FDA-approved for this use.

About 4 children with ADHD, 3 received medicine as treatment. The American Academy of Pediatrics recommend training parents of young children in behavior therapy before prescribing medicine. Also points out very important actions of the federal government, health professionals and parents getting training in behavior therapy, Centers for Disease Control and Prevention –CDC, on National Center on Birth Defects and Developmental Disabilities (2016).

In Australia, methylphenidate and amphetamines are recommended as first-line treatments, while in Canada, a long-acting methylphenidate, amphetamines, and atomoxetine are so regarded (Hodgkings, Shaw, Hetchman, 2012)

In Europe, psychoeducation and behavioral intervention are recommended as first-line therapy for preschool and school age children with ADHD and moderate impairment. In severe cases that fail to respond to psychoeducation and behavioral intervention, methylphenidate or long-term atomoxetine is the indicated drug treatment. UK treatment algorithms recommend methylphenidate and atomoxetine as first- and second-line treatments respectively (Taylor *et al*, 2004).

In Brazil, first-line medications are long-acting methylphenidate, lisdexanfetamine, and atomoxetine, with clonidine as a second-line alternative. Other drugs, such as bupropion and imipramine, are also widely used. Not all are available through the public health service, the most common being methylphenidate, imipramine, and derivatives. In some regions, caffeine is still being used because it is readily available.

Although ADHD has been firmly established as a disorder that meets the criteria for the validation of psychiatric diagnoses (Robins, Guze, 1970) (Faraone, 2005) the validity of the disorder has been challenged by media, journalists, politicians, and even some medical, as well as nonmedical, health professionals in large-scale anti-medicalization campaigns. From this critics diagnosis, ADHD would be caused by inadequate parenting and schooling in a society with high demands for children's self-control and organization (Buitelaar, Rothenberger, 2004) Concerns are expressed concerning over diagnosis and treatment, particularly the dangers of using psychostimulants. Despite their absence of a clinical, academic basis, such claims have adversely affected acceptance of the ADHD diagnosis and appropriate treatment of children with the disorder (Buitelaar, Rothenberger, 2004) (Faraone, 2005).

To address such concerns and determine the biosafety of such medications, the present study comprises an assessment of the side effects of medications provided by Brazil's public health service to treat ADHD.

METHODS

The objective of this study is to evaluate the side effects of medications used by the municipal public health services of Campinas and Paulinia in the state of Sao Paulo to treat ADHD, methylphenidate immediate release (MPH-IR), methylphenidate spheroidal oral drug absorption system (MPH-SODAS), methylphenidate osmotic release oral system (MPH-OROS), imipramine, caffeine, and drug combinations.

A total of 297 patients with ADHD were evaluated at the pediatric neurological clinic of the Universidade Estadual de Campinas' Research Laboratory in Learning Disabilities and Attention Disorders and Paulinia's Center of Therapy and Rehabilitation. Inclusion criteria comprised the following: age between 7 and 14 years, diagnosis by an interdisciplinary team, presence of side effects after initial month of use. Side effects during the first month were not considered since most were temporary, minor adaptations to the drug. Patients and relatives completed an open questionnaire about medications used in treating ADHD and the side effects that occurred. (Table1).

RESULTS

Subject age ranged from 7 to 14 years, with 224 males and 73 females. Medications used were distributed as follows: MPH-IR, 168; MPH-SODAS, 37; MPH-OROS, 15; lisdexanfetamine; 12, imipramine, 45; and drug combinations, 20.

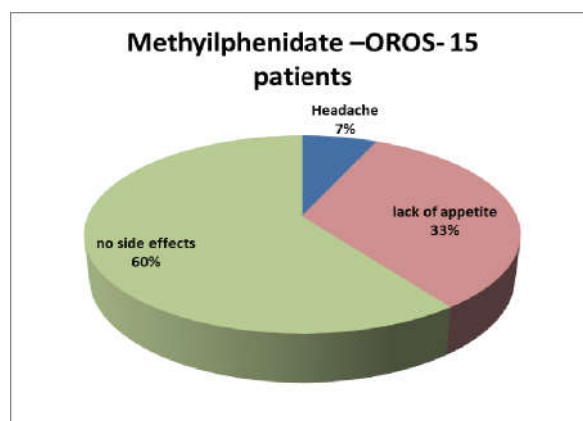


Figure 3

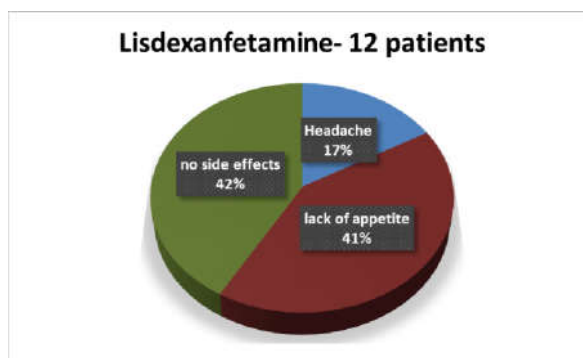


Figure 4

Table 1 Side effects as reported by subjects

Medication	Users	Headache	Sleeplessness	Agitation	Anxiety	Insomnia	Abdominal pain	Lack of appetite
MPH-IR	168	24	4	4	16	3	13	
MPH-SODAS	37	2		2				12
MPH-OROS	15			1				5
Lisdexanfetamine	12	2						5
Imipramine	45		10				4	2
Drugs Combination	20	3	2		3			

*Aggressiveness: was not reported

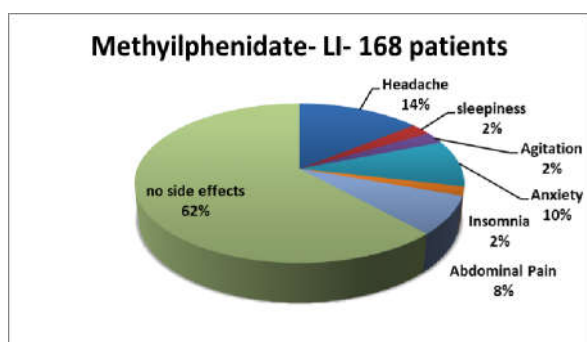


Figure 1

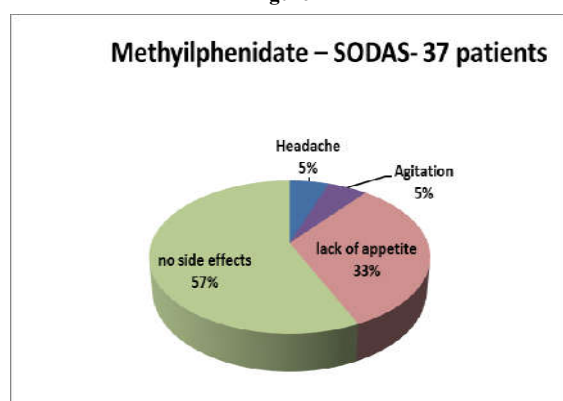


Figure 2

Of the 168 subjects using MPH-IR, 55 (35.7%) presented side effects, with 8 patients presenting more than one. The most frequent were headache, anxiety, and abdominal pains. Of the 37 using MPH-SODAS, 16 (43.2%) presented side effects, with lack of appetite, agitation, and headache most common. Among the 15 using MPH-OROS, 6 (40.0%) presented side effects, with 5 presenting lack of appetite and 1 agitation. Among the 12 using lisdexanfetamine, 7 (58.3%) presented side effects, with 5 presenting lack of appetite and 2, a headache. Of the 45 subjects using imipramine 14 (31.1%) presented side effects, with 2 presenting more than one complaint, abdominal pain and lack of appetite. Of the 20 using a combination of drugs, 7 (35.0%) presented side effects, chiefly, headache, anxiety, and sleeplessness.

DISCUSSION

The treatment of ADHD is challenging and often involves medication integrated with other support therapies such as clinical and educational psychology, behavioral intervention, and speech therapy, among others, depending on the patient's needs (Sax, Kautz, 2003) (Barkley, 2004) (Sonuga-Bark *et al* 2011).

There has been considerable discussion in the literature about the use of particular medications in treating ADHD and their side effects (Knipp, 2006) (Kim *et al*, 2010), but few studies

have evaluated the spectrum of first-line drugs used in its treatment in a comprehensive manner.

Use of MPH-OROS does not usually alter the sleep pattern, but it may, in some cases, improve the sleep of ADHD patients who experience disturbance in initial sleep (Kim *et al*, 2010). Tobaiqy and colleagues found a larger number of subjects experienced side effects (66%) because they used the open questionnaire used in this paper combined with a checklist (Kim *et al*, 2010). For methylphenidate, the most frequently reported side effects were loss of appetite (34.3%), headache (17.9%), mood and emotional problems (14.9%), stomach upset (14.9%), sleep disturbance (10.4%), and rash and other skin problems (5.2%). The checklist listed 467 possible side effects, and the most frequently reported were mood and emotional problems (28.1% [131/467]), stomach and abdominal problems (13.3% [62/467]), insomnia (12.8% [60/467]), and lack of appetite (12.6% [59/467]). The checklist identified a broader range of potential side effects than those reported as free-text.

The literature reports several common adverse effects associated with the use of methylphenidate and amphetamines (Hodgkins, Shaw, Hetchman, 2006) (Pliszka *et al*, 2006). Over 10% of patients using methylphenidate present fatigue, loss of appetite, irritability, and anxiety. Among users of mixed amphetamine salts, the principal complaints were stomach pain, irritability, anxiety, loss of appetite, fatigue, and headache.

In crossover studies, appetite suppression and insomnia were commonly reported as the most common for both stimulants, with elevated rates at higher doses (Hodgkins, Shaw, Hetchman, 2006).

Sonuga-Barke and colleagues (Sonuga-Barke *et al*, 2011) used the Barkley Stimulant Side Effects Rating Scale (BSSERS) BSSERS has six factors: sleep/appetite, dizziness, pain, emotionality, disengagement, and lack of interest. Treatment effects were found only for emotionality, which improved, and sleep and appetite, which worsened. Adverse events were not predictable from subjects' personal and clinical characteristics. Sleep/appetite adverse events were not associated with therapeutic effects. Improvements in attention-deficit/hyperactivity disorder (ADHD) and emotionality were correlated (Sonuga *et al*, 2009).

A frequent concern raised by parents relates to children's growth. Prolonged medication with short-acting MPH has been shown to have minimal impact on height during the first 6 months of use; however, catch-up growth was detected during adolescent period (Moungnoi, Maipang, 2011).

The present study found a low rate of use of long-term methylphenidate, i.e., MPH-OROS, MPH-SODAS, and lisdexamfetamine. This may arise from the impact of their higher costs on the public health budget. Similar reasons may contribute to the use of such second-line medications as imipramine and caffeine.

This study delineates the principal side effects of medications used by the public health system to treat persons with ADHD in Brazil. The results, which are further substantiated by using an open questionnaire rather than a checklist, evidence that these medications are generally safe.

CONCLUSION

In Brazil, as in many other countries, methylphenidate is the most commonly used medication for treating ADHD. It is a relatively safe drug with few side effects, which can be reduced even further by using long-term formulations.

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