

The Treatment of Dual ADHD: a Drop in the Ocean

Tratamiento del TDAH Dual: una Gota en el Desierto

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Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental illnesses in childhood (Polancyk et al., 2007). ADHD can continue into adulthood in around half the patients (Lara et al., 2009) and with a prevalence in this population of between 2.5 and 5% (Kessler et al., 2006, Simon et al., 2009). Some studies suggest that ADHD can have negative impacts at academic, work, social, legal and family levels (Biederman et al. 2012; Klein et al. 2012; Manuzza et al. 2008). Furthermore, childhood ADHD has been linked to an increased risk of substance use in adolescence and adulthood (Carach et al., 2011; Lee et al., 2011). According to population studies, 15% of adult ADHD patients may be affected by substance use disorder (SUD) (Kessler et al., 2006). Among clinical samples, the frequency of SUD is even higher, with some studies describing that at some point in their lives up to 50% of adult ADHD sufferers may develop cannabis dependence, (Torgersen et al., 2006), 45% alcohol abuse or dependence (Biederman et al., 1998), 40% nicotine addiction (Pomerleau et al., 1995), 21% cocaine addiction (Lambert & Hartsough, 1998), and 30% addiction to other substances (Wilens, 2004). Similarly, 23% of SUD patients have comorbid ADHD (van Emmerik-van Oortmerssen et al., 2012). Patients with both ADHD and SUD tend to have a worse prognosis than those who are diagnosed with only one of the two. Indeed, the presence of ADHD in SUD patients has been associated with earlier initiation of substance use, greater consump-

tion and poorer response to treatment (Pérez de los Cobos et al., 2014). The presence of SUD in ADHD sufferers has been linked to an increased risk of criminal behaviour and death by accident (Mannuzza et al., 2008; Dalsgaard et al., 2015). Various theories have been put forward in an attempt to clarify the relationship between ADHD and the development of SUD. This link could be explained by the problems that ADHD patients have to control their own urges, which could lead to increased substance use and the subsequent risk of developing a SUD (Urcelay & Dalley, 2012). It could also be the case that ADHD patients use drugs of abuse to alleviate ADHD symptoms, and given repeated use these drugs create a dependence. This is known as the self-medication hypothesis (Khantzian, 1985; Wilens et al., 2007). In both cases, efficacious treatment of ADHD could reduce drug consumption and improve the SUD. Other factors which have been shown to be involved in the link between ADHD and SUD is the presence of a behaviour disorder and the academic and social impairment associated with ADHD (Molina & Pelham, 2014). Although ADHD and SUD comorbidity is common, little is known as to the efficacy of pharmacological and psychological treatments of either ADHD or SUD among dual patients (Koesters et al., 2009; Pérez de los Cobos 2014), and it is therefore not surprising that these patients do not take easily to treatment for ADHD (Grella et al., 2001; Rowe et al., 2004). With regard to the pharmacological treatment of ADHD in dual patients, a systematic review and meta-anal-

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ysis of randomized clinical trials (RCT) of pharmacological treatments for ADHD implemented on patients with ADHD and substance addiction has recently been published (Cunill et al., 2015). The review identified and included 13 studies with a total of 1,271 patients, and the majority of the RCTs were independent and carried out in USA. The main variables analysed were improvements of ADHD symptoms (assessed by the researcher, self-assessed by the patients and assessed globally), withdrawal from the substance (assessed with objective measurements such as urine tests for drugs and the presence of carbon monoxide (CO) in exhaled air, self-reported by the patient and assessed globally) and treatment discontinuation, defined as the proportion of patients abandoning treatment for whatever reason. These analyses were carried out for all pharmacological treatments and for the different substances abused, in a stratified manner according to the pharmacological treatment and the type of SUD. Five pharmacological treatments were studied: methylphenidate, atomoxetine, pemoline, bupropion and lisdexamfetamine, with a treatment duration of 3 to 16 weeks (mean: 12 weeks). The types of SUD under study were: dependence on nicotine, cocaine, amphetamines, cannabis, alcohol, opioids and also non-specific SUD. Given that in almost half the studies a high risk of bias was detected, mainly due to a high drop-out rate which meant having to work with imputed data sets, the studies were considered to be of low quality methodologically. In addition, bearing in mind that the pharmacological treatments used for ADHD have marked behavioural effects, it cannot be ruled out that the double blind masking of the treatments under study may have failed, leading to possible treatment and detection bias. In terms of results, the meta-analysis found that the pharmacological treatments for ADHD were efficacious in alleviating the severity of ADHD symptoms in patients with SUD (OR= 1.93, 95% confidence interval (CI 95%): from 1.40 to 2.66; $p < 0,001$) both when the assessment was carried out by the researcher or the patient. On stratifying the efficacy results with ADHD symptoms according to the type of pharmacological treatment, it was found that methylphenidate and atomoxetine were more efficacious than placebo, but no differences were found between bupropion, pemoline or lisdexamfetamine and placebo. Results by SUD revealed that pharmacological treatment improved ADHD symptoms in patients with nicotine and alcohol addiction, and in those with a non-specific SUD, but not in those with cocaine, amphetamine or opioid dependence. With regard to the efficacy in treating SUDs, pharmacological approaches did not prove to be any better than placebo in increasing substance abstinence (OR: 1.09; CI 95%: 0.84 to 1.40; $p = 0.529$) irrespective of the type of SUD or treatment. These results were congruent both for objectively assessed and self-reported abstinence. Nor were differences found between pharmacological treatments and placebo in terms

of drop-out rates (OR: 1.14, CI 95%: from 0.88 to 1.48, $p = 0.33$), independently of the type of treatment of SUD. There are at least three possible explanations for these none too favourable results which could be of use in the design of future RCTs. The first of these is of a methodological nature and related to the high response rate observed among placebo patients, which would make the detection of a treatment effect more difficult in the group receiving pharmacological treatment. The placebo group's high response rate could be due to the fact that these patients were receiving concomitant psychotherapeutic treatment which may have given rise to a positive effect on ADHD symptoms and substance consumption (Pérez de los Cobos et al., 2014). The second reason could be that the doses studied were insufficient for the treatment of dual ADHD patients. A recent RCT carried out on patients with ADHD and cocaine addiction which assessed the efficacy of two doses of mixed amphetamine salts (60 and 80 mg/d) in comparison with placebo over 13 weeks found that the reduction in cocaine use over the course of the study and the proportion of patients managing to stay off the drug in the last three weeks of the study was greater in the group taking the 80 mg/d dose of MAS than among those on 60 mg/d and the placebo patients (Levin et al., 2015). Another RCT which compared the efficacy of high doses of OROS methylphenidate (180 mg/d) with placebo over 24 weeks in male patients with ADHD and amphetamine addiction found that methylphenidate was more efficacious than placebo in improving ADHD symptoms, amphetamine consumption and drop-out rate (Konstenius et al., 2014). The third and final explanation is an attempt to give an account specifically of the results observed regarding substance withdrawal. Even if the SUD is a consequence of ADHD, a small improvement in ADHD symptoms would not have a strong enough effect to bring about a reduction in substance use. Two recent results support this possible explanation. Firstly, a secondary analysis of an RCT assessing the efficacy of OROS methylphenidate in combination with nicotine patches in adult ADHD patients with nicotine dependence found that the methylphenidate achieved higher abstinence rates among those patients who had greater ADHD symptoms reduction (Nunes et al., 2013). Similarly, in the meta-analysis described above a positive correlation was also found between abstinence assessed using objective methods and the efficacy on ADHD, which would support the hypothesis that the greater the improvement in ADHD symptoms, the greater the withdrawal from substances of abuse (Cunill et al., 2015). Although, as has been outlined so far, information regarding the efficacy of pharmacological treatment of ADHD in dual patients is scarce, with serious methodological limitations and somewhat poor results, it can be said that this situation is like an oasis of scientific evidence when compared to the information available on SUD treatment efficacy in patients with dual ADHD, where

we only have observational studies and indirect inferences derived from studies on other populations. Given that ADHD has a negative influence on drug consumption, it is not possible to extrapolate results obtained in other populations without this disorder, and therefore vital that studies be carried out on patients with both ADHD and SUD. The situation regarding the scientific evidence available for psychological treatment among patients with dual ADHD is even more discouraging than that for pharmacological treatment given that there is not a single quality RCT which has investigated the efficacy of psychotherapy in dual patients with ADHD. At this point we need to ask why there are so few RCTs with dual ADHD patients. A possible explanation may be the lack of interest on the part of the pharmaceutical industry to carry out studies with complex patients, such as those with comorbid disorders, once treatment authorization is granted, and this is probably due to a lack of incentive since the regulating agencies do not demand it. In fact, the European Drug Agency (EMA) itself recommends the exclusion of SUD patients from pivotal RCTs of new pharmaceuticals being developed for the treatment of ADHD patients (EMA, 2010). It is unsurprising, therefore, that there are many RCTs with ADHD patients generating redundant information and whose sole *raison d'être* is of a commercial nature, while at the same time we lack studies in dual patients (Cunill et al., 2015; Storebo et al., 2015). In the absence of private funding, studies with such patients need to be financed independently, with all the difficulties this involves. In addition, given the complexity of these patients, the high likelihood of unfavourable results may discourage researchers or public agencies from carrying out RCTs on this population.

In sum, the few studies available show that the treatment of ADHD among dual patients results in modest improvements in ADHD symptoms, with a smaller effect size than that observed in patients without SUD (Cunill et al., 2016), without reducing substance consumption nor treatment retention. The review of available studies on patients with dual ADHD, the aim of which was to draw up clinical practice guidelines for the treatment of dual pathology in the adult population (San & Arranz, 2016), has for the first time allowed the formulation of treatment recommendations for patients with ADHD and SUD. Based on the results of this review, we have concluded that pharmacological treatment can be recommended for ADHD to reduce the severity of ADHD symptoms in patients with ADHD and SUD, although this recommendation is weakened by the low quality of the studies available. Conversely, we cannot recommend pharmacological ADHD treatment in order to reduce substance consumption or drop-out rates. Nor can we make any recommendation with regard to the psychological treatment of ADHD nor the treatment of SUD in patients with dual ADHD, given that there are no RCTs focusing on the efficacy of such treatments in dual patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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