Review

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Pharmacological treatments for obsessive-compulsive disorder in children and adolescents: A qualitative review

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We present the results of a systematic review on the effectiveness of pharmacological treatments for children and adolescents with obsessive-compulsive disorder. Sixty-four studies fulfilled the selection criteria, being the most of them focused in SSRI and Clomipramine. The trials on augmentation strategies and third line monotherapies are scarce, being the majority open-trials and case series. Similarly, studies on combined treatment (psychological and pharmacological) are few; furthermore this is a relevant future research line. It is also remarkable the lack of quasi-experimental and experimental comparison studies and the long-term follow-up measures.

Key words: Medication, Obsessive-compulsive disorder, Children, Adolescents

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Pharmacological treatments for obsessive-compulsive disorder in children and adolescents: A qualitative review

Se presentan los resultados de un estudio de revisión sistemática sobre la eficacia de los tratamientos farmacológicos utilizados en el trastorno obsesivo-compulsivo en niños y adolescentes. Sesenta y cuatro estudios cumplieron los criterios de selección, estando en su mayoría centrados en la eficacia de los ISRS y Clomipramina. Los estudios sobre estrategias de potenciación, monoterapias de tercera línea son pocos, tratándose mayoritariamente de diseños abiertos y series de casos. De igual modo, los estudios sobre tratamiento combinado (farmacológico y psicológico) son escasos, siendo una línea importante de cara a la investigación futura. Se constata la baja representación de estudios de comparación tanto cuasi-experimentales como experimentales, al igual que la escasez de medidas de seguimiento a medio y largo plazo.

Palabras clave: Fármacos, Trastorno obsesivo-compulsivo, Niños, Adolescentes

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INTRODUCTION

Obsessive-Compulsive Disorder (OCD) in children and adolescents is relatively frequent. The DSM-IV-TR[1] reports a global prevalence of 1 to 2.3% and annual prevalence of 0.7% in children/adolescents. OCT incidence was studied in Spain in a sample of 18-year old subjects, finding 0.7% based on the DSM-III-R criteria and 1.4% when following the ICD-10[2] approach.

The consequences of this disorder are enormously severe on the life of children/adolescents, interfering in their personal, social, school and family life.[3,4] On the other hand, many studies have found elevated comorbidity rates, finding that up to 80% of children have some associated disorder. These comorbid disorders increase the grade of interference, worsen the course of the disorder and limit response to treatment.[5]

The important repercussions that OCD has on the life of children and adolescents have induced the investigators to elaborate evaluation instruments and to improve the therapeutic interventions on the psychological and pharmacological level. Given the proliferation of treatment studies in recent years, we have aimed to carry out a qualitative review of those that have used a drug in children and adolescents with OCD as principal treatment. Even though recent meta-analysis studies[6,7] and qualitative review[8,9] studies have been carried out, we consider that our review is justified for the following reasons: (1) The recently performed qualitative review studies done are partial. Specifically, the most recent study[8] focused on antidepressants and did not include 11 studies on these drugs that we include in our research in their review. On the other hand, the Mancuso et al.[9] study only presented the randomized designs in the section of drugs studies. They did not include the rest of the investigations. (2) We include the studies of combined treatments (drugs together with cognitive-behavioral therapy (CBT). (3) We present an up-dated summary of the augmentation studies and third line monotherapies.

METHOD

Screening criteria

The conceptual and methodological criteria that we used to be able to include a research report with rigor are the following: (a) The study should be focused on the application of a drug in minor subjects diagnosed of OCD using internationally recognized procedures, that is DSM-III[10] and subsequent versions[1,11,12] and/or ICD-9,[13] ICD-10.[14] (b) Sample size in the posttest should be equal to or greater than 4. (c) The studies should be written in English, French, Italian or Spanish and performed between 1970 and the first quarter of 2012.

Search strategies

First, a computerized search was conducted using the Medline/PubMed, EMBASE, SCOPUS, Academic Google and *Cochrane Plus* library. This search included the years 1970-2012, with the key words in English: *Obsessive compulsive, OCD, treatment, trial, selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), pediatric, child** and *adolesc**; and the same words in Spanish search in the title and abstract. Second, the references of meta-analysis and systemic review on the subject were reviewed. Sixty four articles fulfilled the screening criteria, three being excluded as they did not present efficacy data.

Information analysis

The studies were classified into four groups: 1) studies on tricyclic antidepressants (*n*=8), 2) on selective serotonin reuptake inhibitors (*n*=35), 3) on drug augmentation and third generation monotherapies (*n*=10) and 4) combinations of drug treatment and CBT (*n*=8).

RESULTS

Tricyclic antidepressants

Clomipramine was first evaluated for use in this disorder in 1967.[15] This drug has been tested using different types of designs so that it was possible to verify its superiority in pre-posttest designs,[16] with a placebo control condition,[17,18] with cognitive behavior therapy[19] and with another tricyclic antidepressant, desipramine.[20-23] The latter finding made it possible to establish clomipramine as the only agent of this group that has adequate properties for the treatment of OCD. The differential efficacy of this substance has also been compared in children versus adults[16] concluding that in spite of response to treatment of both groups, adults obtained significantly better benefits. On the other hand, follow-up, substitution or crossed design studies have shown that there is a higher rate of relapse of the subjects after the drug is discontinued.[24] Finally, the side effects observed in the studies are mostly derived from the anticholinergic effects of clomipramine, which have not been severe in the trials described. Table 1 shows the principal characteristics of these studies.

SSRI

Table 2 shows the most outstanding data of the studies conducted on these drugs.

Fluoxetine

It is one of SSRIs to be studied among the first ones to be approved by the FDA in 1988 and subjected to controlled testing for child/adolescent OCD, showing high efficacy.[25] Extensive research has been carried out with this drug in relation to pediatric OCD, in studies performed in a controlled and quasi-experimental way. The first outstanding aspect is the efficacy observed in all the studies. Improvement percentages of approximately 50% with the use of 20 to 60 milligrams daily were achieved.[26-33] Higher doses have provided higher improvement percentages. However, most of the participants of this study received other concomitant treatments.[29] Furthermore, fluoxetine is generally shown to be more effective than the placebo pill[25,33,34] except for in one of the experimental trials. However, although in the latter study the drug was used to treat obsessions and compulsions, the primary diagnosis was Tourette syndrome.[35] As occurs with other drugs, the relapse percentage after withdrawal of fluoxetine was elevated, this varying from 43.5 to 50%.[25,31] Fluoxetine was used in pre-school children in two studies.[36,37] The dose used in this group was low (5 and 20 mg/day) achieving pretest/posttest improvements.

Sertraline

Sertraline has also been studied widely in this setting in investigations performed with different methodologies. These studies have generally reported good results, the response percentage varying from 21.4% to 100%. Furthermore, some of the studies have reported an average reduction in symptoms of approximately 50%.[38,39] On the other hand, two studies have shown that treatment with sertraline is more effective than the placebo pill.[40,41] Regarding the differential efficacy of this agent compared to cognitive-behavioral treatment, significant differences were not found in these studies.[41,42] However, once the treatment period was completed, the number of relapses by the subjects in the medication group was much greater than that observed in the CBT group.[42] On the other hand,

Table 1 Clomipramine treatment evaluation studies

Study	Design	Dose /duration	Results
Rapoport et al. (1980) N=9	Clomipramine Desipramine Placebo	50-150 mg/day 16 weeks	No significant differences between the groups. Significant pretest posttest improvements in the three groups
Flament et al. (1985) N=19	Clomipramine Placebo	141 mg/day 5 weeks	Significant differences in favor of clomipramine
Leonard et al. (1988) N=21	Clomipramine Desipramine	3 mg./Kg 5 weeks	Significant differences in favor of clomipramine
Leonard et al. (1989) N=48	Clomipramine Desipramine	3 mg/Kg 10 weeks	Significant differences in favor of clomipramine
Leonard et al. (1991) N=28	Clomipramine Desipramine	50-250 mg/day 8 months	Significant differences in favor of clomipramine Relapse during substitution
De Veaugh-Geiss et al. (1992) N=60	Clomipramine Placebo	25-100 mg/day 8 weeks	Significant differences in favor of clomipramine
De Haan et al. (1998) N=22	Clomipramine CBT	25-100 mg/day 5 weeks	Significant pretest-posttest improvement Significant differences in favor of CBT
Ulloa et al. (2007) N=15	Clomipramine	50-225 mg/day 8 weeks	Significant pretest-posttest improvement

Table 2 SSRI treatment evaluation studies

Study	Design	Dose / duration	Results
Liebowitz et al. (1990) N=8	Fluoxetine	20-80 mg/day 8 weeks	Response in 50% of the patients
Riddle et al. (1990) N=10	Fluoxetine	10-40 mg/day 20 weeks	Respuesta en el 50% de los pacientes
Como y Kurlan (1991) N=13	Fluoxetine	20-40 mg/day 7 months	Significant pretest-posttest improvement
Riddle et al. (1992) N=14	Fluoxetine Placebo	20 mg/day 20 weeks	Significant differences in favor of Fluoxetine Relapse of 50% after switching to placebo in crossing of groups
Kurlan et al. (1993) N=11	Fluoxetine Placebo	20-40 mg/day 16 weeks	Significant improvement in both groups. No differences between both
Reed et al. (1995) N=38	Fluoxetine	50 mg/day 14-34 months	Significant pretest-posttest improvement
Geller et al. (1995) N=38	Fluoxetine	50 mg/day 19 months	Significant pretest-posttest improvement
Vertucci et al. (1995) N=8	Fluoxetine	20-60 mg/day 50 days	Reduction of 50% in half of the subjects
Baysal y Ünal (1996) N=5	Fluoxetine	20 mg/day 5 months	Significant pretest-posttest improvement
Semerci y Unal (2001) N=23	Fluoxetine	20 mg/day 20 weeks	Significant pretest-posttest improvement Relapse in 43.5% between 8 and 16 weeks of drug withdrawals
Geller et al. (2001) N=103	Fluoxetine Placebo	20-60 mg/day 13 weeks	Significant differences in favor of Fluoxetine
Liebowitz et al. (2002) N=43	Fluoxetine Placebo	20-80 mg/day 16 weeks	Significant pretest-posttest improvement Fluoxetine at 16 weeks

Tabla 2 **Continuation**

Coskun y Zoroglu (2009) N=6	Fluoxetine	5-15 mg/day 10 weeks	Significant pretest-posttest improvement in 5 children
Ercan et al. (2012) N=4	Fluoxetine	10-20 mg/day 8 weeks	Pretest-posttest improvement
Johnson (1993) N=5	Sertraline	200 mg/day 41 days	Significant pretest-posttest improvement
Rodríguez-Ramos y Mardomingo (1998) N=8	Sertraline	50-200 mg/day 6 months	Significant pretest-posttest improvement. Mean reduction of 46.7%
Alderman et al. (1998) N=17	Sertraline	25-200 mg/day 5 weeks	Significant pretest-posttest differences No differences according to dose received
March et al. (1998) N=187	Sertraline Placebo	167 mg/day 12 weeks	Significant differences in favor of sertraline. Response in 42%
Cook et al. (2001) N=132	Sertraline (seguimiento)	120-132 mg/day 52 weeks	Response to drug in 67% patients
March et al (2004) N=112	Sertraline CBT Sertraline + CBT Placebo	25-200 mg/day 12 weeks	Sertraline was significant more effective than the placebo, equal to the CB and less than mixed treatment
Ramos-Asbarh et al. (2005) N=20	Sertraline CBT	25-200 mg/day 12 weeks	Significant pretest-posttest improvement both interventions No significant differences between the groups
Alderman et al. (2006) N=43	Sertraline	50-200mg/day 24 weeks	Significant reduction of 49% patients
Rosenberg et al. (1999) N=20	Paroxetine	10-60 mg/day 12 weeks	Significant pretest posttest improvement. Reduction of 29.4%
Diler y Avci (2000) N=47	Paroxetine	20 mg/day 12 weeks	Significant pretest posttest improvement. Mean reduction of 50%
Geller et al. (2003) N=335	PHASE 1 Paroxetine PHASE 2 (N = 193) Paroxetine Placebo	10-60 mg/day FASE 1 16 weeks FASE 2 16 weeks	PHASE 1 - response of 71% PHASE 2 - 10% more recurrences in plus several
Geller et al. (2004) N=203	Paroxetine Placebo	10-50 mg/day 10 weeks	- Significant differences paroxetine
Apter et al. (1994) N=14	Fluvoxamine	100-300 mg/day 8 weeks	Significant pretest posttest improvement
Riddle et al. (2001) N=120	Fluvoxamine Placebo	25-200 mg/day 10 weeks	Significant differences in favor of fluvoxamine Mean reduction of 24.6%
Walkup et al. (1999) N=99 (seguimiento Riddle et al., 2001)	Fluvoxamine	200 mg/day 12 months	Mean reduction of 42%
Thomsen (1997) N=23	Citalopram	10-40 mg/day 10 weeks	Significant pretest posttest improvement Elevated response in 17.4% and moderate in 60%

Table 2 Continuation

Thomsen et al. (2001) N=30	Citalopram	20-70 mg/day 24 months	Significant improvement after 10 weeks
Toros et al. (2002) N=23	Citalopram	10-20 mg/day 8 weeks	Significant pretest-posttest improvement
Mukaddes et al. (2003) N=15	Citalopram	10-30 mg/day 8 weeks	Significant pretest posttest improvement. Reduction superior to 50% in 80% of the sample
Alaghband-Rad y Hakimshooshtary (2009) N=29	Fluoxetine Citalopram	20 mg/day 6 weeks	Significant pretest posttest improvement in both groups. No significant differences between the groups

sertraline alone is significantly less effective than when combined with CBT.[41] Regarding drug dosage, the amounts administered daily are superior to those used with other SSRIs. These begin with initial doses of 25 to 50 mg/day, with increases up to a maximum of 200 milligrams daily. Some authors[43] have not found differences en relation to the 25 and 50 mg/day dose used. The studies have reported mild and moderate severity adverse effects.

Paroxetine

Efficacy of paroxetine to treat pediatric OCD has been evaluated on four occasions. Pretest-posttest studies have reported significant improvements with reduction in measurements of obsessions and compulsions from 29% to 50%.[44,45] In the experimental studies, paroxetine has been shown to be superior to placebo both when the studies have directly evaluated their efficacy to improve OCD[46] and when attention has been given to the percentage of relapses in subjects who have previously responded to the drug and have then been switched to the placebo.[47] Initial doses used have varied from 10 to 20 milligrams daily, with a maximum dose used being 60 mg/day. Its adverse effects are similar to those of other SSRIs.

Fluvoxamine

Fluvoxamine has been among the drugs approved by the FDA to treat child-adolescent OCD since 1994. Fluvoxamine has only been tested in two independent samples of children/adolescents with OCD. In both cases, the drug was shown to be significantly effective.[48,49] On the other hand, it has been observed that the average reduction of the symptoms increases the longer the drug has been administered, going from 25% at 10 weeks of treatment to 42% at one year of consumption.[49,50] In general, intervention is initiated with administration of a 25 mg daily dose, which is subsequently titrated up in 50 mg increments, with the possibility of reaching a maximum of 300 mg per day if required by the course of the disorder. The appearance of adverse events that generally are not very important must also be kept in mind.

Citalopram

As fluvoxamine, citalopram is one of the least studied selective inhibitors. In addition, its efficacy has not been evaluated against a control group. However, there are several studies of a single group[51-54] or comparison of two drugs[55] performed in this regards that provide promising results on its safety and efficacy. The results show the existence of significant improvements in the subjects once they have received the treatment. This means that this drug is shown to be promising alternative pending the comparison of its efficacy with that provided by a placebo control group. Its adverse effects have been tolerable in the studies performed up to now.

Other pharmacological strategies

The use of other pharmacological strategies is considered after failure of the treatment of first choice (absence of clinical response or partial response generally evaluated with a severity or intensity scale of the obsessive-compulsive symptoms or clinical impression scale, for example the *Clinical Global Impression*). These strategies may be augmentation of the SSRI drug and third line monotherapies. Drugs that have most frequently been added to potentiate the effect of the SSRIs are tricyclic antidepressants -clomipramine-[56,57] and atypical antipsychotics -risperidone, aripiprazole.[58-60] Anxiolytics -buspirone-have also been used.[61] All of these have provided improvements in the patients.

In regards to third line monotherapy, we must indicate that these should be considered when both first choice treatments as well as augmentation strategies have been shown to be ineffective. One of the drugs used has been ziprasidone, an atypical antipsychotic drug,[62] although other

therapies such as plasma exchange.[63,64] or the administration of glutamate antagonists[65] have also been tested.

Combination of pharmacological treatment and CBT

Very few studies have combined psychological therapy and drug treatment. Those performed have aimed to observe if the child/adolescent improved when CBT was introduced along with the medication[66-71] SSRI or clomipramine. One of the combinations that has the most support is CBT together with sertraline, which has been demonstrated to be significantly superior to drug therapy and CBT alone.[41] Recently, a study that was complementary to the previous one[68] compared the results on adding CBT to drug treatment (SSRI), concluding that children treated with complete CBT and medication achieved greater reductions in their obsessive symptoms. The latest study is with the addition of D-cycloserine to CBT in a recent trial carried out by Storch et al.[72] that obtained very promising results.

CONCLUSIONS

The experimental evidence in the drug field has great empirical support, as controlled studies have been performed in most of these drugs. These studies have shown an adequate efficiency level to reduce obsessive-compulsive manifestations in children/adolescents. SSRIs constitute the first choice since although their effects are less potent than clomipramine, they show a greater degree of safety and tolerability and do not present the cardiotoxic effect of the classically antidepressants.[17,25,33,34,49]

In addition to this high level of tolerability, there is also evidence regarding their beneficial effects on disorders that are frequently associated to OCD.[27,30,35] One of their disadvantages is that the percentage of relapses is high when the drug is discontinued.

In regards to the differential efficacy of the SSRIs, there is a lack of comparison studies between the different drugs since we only find one comparison study between fluoxetine and citalopram.[55] Differences have not been found for action rate, since children/adolescents treated with fluvoxamine begin to respond between the fourth and sixth week. [48] The same occurs regarding those treated with sertraline, who improve beginning with the fourth week.[40] Finally, studies conducted with paroxetine reported improvements between the fourth and sixth week.[44,45] Few studies have been performed with middle to long term follow-ups. One has been found on clomipramine,[21] two on fluoxetine,[27,29] two on sertraline,[39,73] one on fluvoxamine[50] and one on citalopram.[53] In these, it has been observed that maintenance of the drug improves obsessive-compulsive symptoms. The only drug used in pre-school children is fluoxetine at low doses, producing significant improvements.

The studies on augmentation strategies and third line monotherapy in the pediatric population are mostly open designs and case series. Therefore, research and use of control designs are still lacking to determine the efficacy of these groups of therapies.

Regarding combination of drug therapy and CBT, experimental studies have reported more effective results than the two isolated interventions. However, because there are few studies, no definitive conclusions can be reached. However, this may be one of the future strategies. Finally, it should be remembered that some of the studies had important methodological limitations (for example, lack of a control group, use of different selection criteria for the participants, small sample sizes, absence of follow-up data, etc.) that hinder accurate evaluation of the benefits of some of the interventions.

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