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Antidepressant Drug Treatment in Child and Adolescent Psychiatry

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Abstract

Antidepressants are commonly used psychiatric drugs for a wide variety of Psychiatric disorders. Their use in children and adolescents has however been controversial despite unequivocal demonstration of benefits in some children with serious mental illnesses. This review was completed to evaluate available research in children and adolescents with depression and anxiety. Given the lack of long term randomised control studies, naturalistic studies could offer a way to evaluate efficacy among antidepressants.

Aim: To evaluate randomised control studies and naturalistic studies to investigate the classes of antidepressant medications, and their associated efficacy, tolerability, and safety in paediatric psychiatry.

Method: A review of randomized controlled trials and meta-analyses of antidepressant medications in paediatric populations for the treatment of a wide range of mood and anxiety psychiatric disorders was conducted. A subsequent review of the available naturalistic studies for antidepressants in this population was carried out.

Conclusions: The review highlighted the paucity of studies available and the need for naturalistic studies in diagnostically heterogeneous paediatric populations receiving antidepressant drug treatment.

Introduction

Since the late 1990s, there has been a substantial increase in the use of antidepressant drug treatment in child and adolescent psychiatric care [1]. Although regulatory warnings prompted in a decline in paediatric antidepressant use from 2003 to 2005, their use has since rebounded [2]. And while most products have not been approved for use in this population, off-label use of antidepressants is widespread practice [3] regulatory warnings have led to changes in antidepressant use that might have differed across various countries. Our study aimed at determining factors associated with antidepressant prescribing practices and at assessing trends in use from 1997 to 2005 in Quebec youth.A retrospective cohort study was conducted through claims databases of the Quebec public health care program (RAMQ. Antidepressants, like all medications, warrant concerns over their efficacy, tolerability, and safety in child and adolescent psychiatry. Generally, antidepressants have several side effects, such as weight gain, fatigue, and sexual dysfunction. However, the availability of a wide diversity of antidepressants support the individualized selection of treatment, allowing clinicians to personalize treatment for their paediatric patients based on psychiatric symptoms and undesirability of certain side effects.

The purpose of this review was to investigate the classes of antidepressant medications, and their associated efficacy, tolerability, and safety in paediatric psychiatry. A review of randomized controlled trials and meta-analyses of antidepressant medications in paediatric populations for the treatment of a range of psychiatric indications, such a major depressive disorder, anxiety disorders, and obsessive compulsive disorder, was conducted. A subsequent review of the available naturalistic studies for antidepressants in this population was carried out. The latter highlighted the paucity of studies available and the need for naturalistic studies in diagnostically heterogeneous paediatric populations receiving antidepressant drug treatment. Lastly, the common methodological and ethical limitations of naturalistic studies was assessed and addressed. The aim of this report was to emphasize the clinical significance of naturalistic studies and to better inform the proposal of a naturalistic prospective study of antidepressant medications in child and adolescent psychiatry.

Antidepressant Drug Treatment

Definition

The term "antidepressants" refers to a chemically and pharmacologically heterogeneous class of psychopharmacological agents originally prescribed to treat patients with depressive symptoms, but are associated with use in a wide array of disorders today. These agents have been successfully applied to the treatment of major depressive disorder (MDD), anxiety disorders, obsessive compulsive disorder (OCD), eating disorders, mutism, and attention deficit/hyperactivity disorder (ADHD). Antidepressants elevate pathologically depressed mood, may increase activity or diminish psychomotor restlessness, and may lessen somatic and vegetative symptoms [4]. Antidepressants are associated with several side effects, including weight gain, sexual dysfunction, and fatigue. Although the mechanism of action of antidepressants is not yet fully understood, most antidepressants primarily inhibit the neuronal reuptake of monoamines (such as serotonin or noradrenalin) from the synapse. Generally, it is recommended antidepressant therapy is continued for 4-6 months after symptoms subside before the dose is reduced or discontinued [4].

Antidepressants are classified according to their recognized biological sites and mechanisms of action: selective serotonin reuptake inhibitors (SSRIs), serotonin and nor epinephrine reuptake inhibitors (SNRIs), nor epinephrine and dopamine reuptake inhibitors (NDRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), and monoamine oxidise inhibitors (MAOIs). Within each class of antidepressants, there are a number of individual agents that differ in their degree of neuronal inhibition, present varying efficacies, tolerability, and safety, and pose distinctive potentials for drug interactions. These side effects of antidepressant treatment can adversely impact patients' compliance and have the potential to influence treatment outcome, morbidity and mortality [5]. It is therefore imperative to quickly determine the most effective agent for a given patient; fortunately the multiplicity of antidepressant agents allows clinicians to better individualize treatment for psychiatric disorders [5].

Classification

SSRIs. This group of drugs, including fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Cipralex), and sertraline (Zoloft), is usually the first choice for treatment of anxiety and depression problems [6]. SSRIs are typically well tolerated drugs associated with less serious adverse events; common side effects include headache, loss of appetite, nausea, diarrhea weight loss, dry mouth, sweating, and disturbances of sexual function [4].

SNRIs. This class of medications includes venlafaxine (Effexor), duloxetine (Cymbalta), and desvenlafaxine (Pristiq). These drugs are typically used to treat depression, anxiety problems, and chronic pain. Because of its efficacy observed in clinical trials in adults, low side-effect profile and early onset of action, venlafaxine is suggested as medication useful for use in children and adolescents [7].

NDRIs. The medication available in this class is bupropion (Wellbutrin, Zyban). Bupropion is often given for energizing effects, in combination with other antidepressants, in the treatment of depression [4]. It is also used to treat attention-deficit/hyperactivity (ADHD) disorder. Common side effects are jitteriness and insomnia.

NaSSAs. The agent available in this class, mirtazapine (Remeron), is the most sedating antidepressant, and is therefore most appropriate for people who have insomnia or who are very anxious [6]. This medication also helps to stimulate appetite. Common side effects are drowsiness and weight gain.

TCAs. This older group of agents is the most extensive of all antidepressant types, comprised of amitriptyline (Elavil), maprotiline (Ludiomil), imipramine (Tofranil), desipramine (Norpramin), nortiptyline (Novo-Nortriptyline) and clomipramine (Anafranil). Common side effects include dry mouth, tremors, constipation, sedation, blurred vision difficulty urinating, weight gain and dizziness. Additionally, because TCAs may cause heart rhythm abnormalities, an electrocardiogram (ECG) is recommended before onset of treatment [6]. Moreover, overdose and intoxication of TCAs is associated with fatal cardiac arrests [4]. Because these medications tend to have more severe side-effects than newer antidepressant classes and they pose an elevated risk of intoxication [8], they are not often a first choice for treatment. However, when other drugs do not provide relief from severe depression, these agents may help.

MAOIs. MAOIs, such as phenelzine (Nardil) and tranylcypromine (Parnate), were the first class of antidepressants. Although effective, MAOIs are often avoided because one must follow a special diet to avoid hypertensive crises associated with the consumption of tyramine-containing foods [4], such as aged cheeses and nuts. A newer MAOI, moclobemide (Manerix), can be used without dietary restrictions; however, it may not be as effective as other MAOIs. Common side effects include a change of blood pressure when moving from a sitting to a standing position (orthostatic hypertension), insomnia, swelling and weight gain [6].

Randomized Controlled Trials of Antidepressant Drug Treatment in Children and Adolescents

SSRIs

In child and adolescent psychiatry, SSRIs have become the primary choice for the pharmacological treatment of anxiety and depressive disorders [9,10,8,11, 4]"given" : "Manfred", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Psychiatric drugs in children and adolescents: Basic pharmacology and practical applications", "id" : "ITEM-1", "issued" : { "date-parts" : [["2014"]] }, "page" : "83-155", "publisher" : "Springer", "publisher-place" : "Vienna", "title" : "Antidepressants", "type" : "chapter" }, "uris" : ["http://www.mendeley.com/documents/?uuid=0f40f195-0a36-4ac5-9b08-3e93b1807390"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1038/mp.2011.150", "ISBN" : "1359-4184", "ISSN" : "1476-5578", "PMID" : "22064376", "abstract" : "Depression and anxiety are common disorders in youth that can have profound influences on functioning and even mortality. In the late 1990s, large controlled trials began demonstrating the efficacy of selective serotonin reuptake inhibitors for these conditions in the pediatric population. By 2003, regulatory agencies began warning the public of unrecognized risk and misrepresented benefit. The current Review summarizes a series of published and unpublished efficacy and safety data regarding antidepressant use in children and adolescents. The resulting complex synthesis suggests that these medications may offer mild-to-moderate benefit, with notable exceptions depending on medication and indication, but they may also heighten the risk for suicidal ideation and parasuicidal behavior. However, reviewed epidemiological data does not demonstrate a relationship between newer antidepressant prescription and completed suicide in large populations of youth. In conclusion, this breadth of mixed research data is applied to clinical decision making.", "author" : [{ "dropping-particle" : "", "family" : "Henry", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kisicki", "given" : "M D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Varley", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular Psychiatry", "id" : "ITEM-2", "issue" : "12", "issued" : { "date-parts" : [["2012"]] }, "page" : "1186-93", "title" : "Efficacy and safety of antidepressant drug treatment in children and adolescents.", "type" : "article-journal", "volume" : "17" }, "uris" : ["http://www.mendeley.com/documents/?uuid=7546f381-4189-4a06-8857-25786feaf27f"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1176/appi.ajp.160.11.1919", "ISBN" : "0002-953X (Print and the use of SSRIs in the clinical treatment has become increasingly common [12, 13]. A Canadian Institute of Health Research (CIHR) funded study in Quebec revealed that SSRIs were the most frequently dispensed (58.8%) antidepressant products among adolescents [3] regulatory warnings have led to changes in antidepressant use that might have differed across various countries. Our study aimed at determining factors associated with antidepressant prescribing practices and at assessing trends in use from 1997 to 2005 in Quebec youth. A retrospective cohort study was conducted through claims databases of the Quebec public health care program (RAMQ. This trend is in large part due to their comparatively good efficacy and tolerability, giving them a favourable benefit-risk profile for paediatric use [14,15,4]. Several controlled studies have indicated that SSRIs are superior to placebo in child and adolescent psychiatric care. Results from a meta-analysis, which included 18 controlled and 23 open trials, suggested a significant benefit of SSRIs over placebo in the treatment of paediatric depression [16]. In the treatment of anxiety disorders (generalized anxiety, social phobia, and separation anxiety), SSRIs have also been shown to reduce symptoms [17,18].

However, in 2004, the United States Food and Drug Administration (FDA) issued a black box warning for antidepressant treatment in children and adolescents. Consequently, Bridge and colleagues (2007) conducted a meta-analysis assessing the use of antidepressants across the indications of depression, anxiety disorders, and OCD in paediatric populations. The review, which included 27 prospective randomized controlled trials (RCTs), estimated suicide risk associated with SSRIs in the treatment of children and adolescents at less than 1% [14]. A more recent meta-analysis maintained no elevated risk for suicidal thoughts or actions in paediatric antidepressant treatment with fluoxetine, citalopram, sertraline, or paroxetine [19]. Nevertheless, a subsequent review by Sparks and Duncan (2013) posits recent investigations on the safety and efficacy of antidepressants contain significant confounds that discredit their findings, and suggests first line prescription of antidepressants for the paediatric population is not advisable and further investigations are warranted.

The most studied SSRI agent in the realm of child and adolescent psychiatry RCTs is fluoxetine. In the treatment of depressive disorder, fluoxetine [9,20,21,22,23,19], sertraline [24,25], citalopram [26] randomized, double-blind, placebo-controlled study compared the safety and efficacy of citalopram with placebo in the treatment of children (ages 7-11, escitalopram [27,28] randomized, double-blind, placebo-controlled trial of escitalopram in adolescent patients with major depressive disorder. METHOD: Male and female adolescents (aged 12-17 years, and paroxetine [29], have all demonstrated superiority over placebo for children and adolescents. Although, results have been inconsistent for some agents. Results of a 2006 RCT indicated that for depression, escitalopram was only beneficial in the treatment of adolescent populations, but showed no superiority over placebo when younger children were included in the analysis [30]. In a more recent RCT, Emslie and colleagues [86] could not replicate the superiority of paroxetine over placebo.

In the treatment of anxiety disorders, fluoxetine [31,32], fluvoxamine [33,34], sertraline [35], paroxetine [36], have all shown greater efficacies than placebo in RCTs. Lastly, in the treatment of pediatric OCD, fluoxetine [37], fluvoxamine [38], sertraline [39,40], and paroxetine [41] have demonstrated efficacy and superiority to placebo.

SNRIs

Extended-release venlafaxine [42] even pediatric patients who are treated successfully during an acute episode may need longer-term treatment. Yet, data on long-term treatment with antidepressants in pediatric MDD are limited. OBJECTIVE: To evaluate long-term effectiveness and safety of treatment with venlafaxine extended-release (ER, duloxetine [43,44], and desvenlafaxine [45], have been proved effective in children and adolescents with depression, although these results have not been consistent. In a separate study, Emslie and colleagues determined that venlafaxine may be effective in depressed adolescents, but not in younger children [42]. Authors did note that those taking venlafaxine were more frequently troubled by suicidal and hostile thoughts, and emphasized that the safety and efficacy of venlafaxine in pediatric patients has not been adequately established. In a subsequent RCT by Emslie and colleagues, results were inconclusive, as neither the investigational drug (duloxetine) nor the active control (fluoxetine) significantly differed from placebo [46]. Similarly, in a placebo-controlled study of 40 children and adolescents with depression, the combination of venlafaxine and psychotherapy was no more effective than treatment with placebo and psychotherapy [47].

For the treatment of childhood and adolescent anxiety disorders, extended-release venlafaxine [48,49] and duloxetine [50], have been shown more efficacious compared to placebo in RCTs. Data on SNRIs for the treatment of child and adolescent ADHD is scarce, a recent review citing only 6 RCTs (5 venlafaxine, 1 duloxetine) [51]. Findings to date however, indicate superiority of venlafaxine to duloxetine, which only demonstrated minimal efficacy in the treatment of ADHD in pediatric populations [51], as well as superiority to placebo [52]. There were no available RCTs assessing desvenlafaxine for child and adolescent psychiatric care other than for depression.

NDRIs

RCTs assessing NDRIs in children and adolescents have focused mostly on ADHD, but have yielded mixed results. In a small RCT assessing bupropion in adolescents with comorbid ADHD and depression, participants exhibited significant improvement and the medication was well tolerated [53]. In two separate randomized double-blind studies, bupropion demonstrated a comparable safety and efficacy profile with methylphenidate (a central nervous system (CNS) stimulant) in children and adolescents with ADHD [54,55]. More recently, however, a meta-analysis determined that bupropion was less efficacious than methylphenidate in reducing ADHD symptoms, and both were inferior to lisdexamfetamine (CNS stimulant) [56]. However, more randomized, placebo-controlled studies of NDRIs in children and adolescent depression are needed.

NaSSAs

In a US Federal Drug Administration (FDA) report on the efficacy of mirtazapine in the treatment of pediatric depression, results of two randomized, placebo-control trials of the NaSSA were published [81]. No statistically significant difference between mirtazapine and placebo was found in either study; there is no evidence that mirtazapine is effective for the treatment child and adolescent depression.

TCAs

In the previously mentioned CIHR funded study of antidepressant use among children and adolescents in Quebec, TCAs were the most frequently dispensed products among children (50.9%) [3]. Nevertheless, there have been few RCTs of the efficacy of TCAs in children and adolescents. Studies thus far have demonstrated TCAs are not significantly superior to placebo in the treatment of paediatric depression or anxiety disorders. An RCT comparing imipramine, paroxetine, and placebo for the treatment of adolescent depression, response to TCA (imipramine) treatment was not significantly different from placebo across any of the seven depression-related variables assessed, moreover study withdrawal due to adverse events occurred in 31.5% of patients treated with imipramine, nearly half of which experienced adverse cardiac events such as tachycardia or arrhythmia [29]. Results from a subsequent meta-analysis assessing the efficacy of TCAs and SSRIs in pediatric populations found TCAs held no significant benefit over placebo in the treatment of depression [16].

In the treatment of children and adolescents with anxiety disorders, clomipramine treatment showed no benefit over placebo for the reduction of anxiety symptoms, although authors noted that placebo response was unusually high [32]. In a meta-analysis of pharmacological RCTs for the treatment of OCD in children and adolescents, TCA treatment (clomipramine) was found to have a significantly greater effect than SSRI treatments in the reduction of OCD symptoms [10]. However, authors posit that clomipramine remains less "user-friendly" in paediatric populations than the SSRIs and due do frequent adverse events and concerns over potential arrhythmogenic events, and suggest that the TCA should not be recommended as a first line treatment for OCD in uncomplicated cases [10].

However, in a review of 6 RCTs for the treatment of ADHD in paediatric populations, TCAs (desipramine, clomipramine, and nortriptyline) outperformed placebo in the reduction of core ADHD symptom severity and there were no serious adverse events reported in any of the included trials [57]. However, Otasowie and colleagues stipulate that the effect of desipramine on the cardiovascular system remains an important clinical concern and therefore evidence supporting the clinical use of desipramine for the treatment of ADHD in paediatric populations is low. Of interest, in the first randomized controlled trial of amitriptyline versus gabapentin for paediatric neuropathic pain, both medications proved similarly effective for decreasing pain scores and improving sleep with no difference in adverse events reported [58] and requires a multimodal approach of pharmacologic, physical, and psychological therapies; however there is little evidence to guide practice. Amitriptyline and gabapentin are first-line drugs for treating neuropathic pain in adults, yet no studies have examined their efficacy, or compared them directly, to

determine which might be better for pain relief and sleep disturbance in children. \n\nMETHODS\nAfter informed consent was obtained, 34 patients aged 7\u201318 years diagnosed with complex regional pain syndrome type I (CRPS I.

MAOIs

There are few recent RCT of MAOIs in the treatment of child and adolescent psychiatric disorders. In one of the earliest studies of antidepressant drug treatment for child and adolescent depression, a double-blind cross-over trial showed that MAOI phenelzine and chlordiazepoxide (a benzodiazepine) were superior to phenobarbitone (a barbiturate) and a placebo [59]. However, in a recent multisite, randomized, variable dose study to evaluate a selegiline transdermal system (STS) for treatment of depression in pediatric patients, neither selegiline nor placebo was found to be statistically superior [60].

There is literature regarding small RCTs that suggest MAOIs may be safe and effective for ADHD in children and adolescents. Two studies comparing MAOI selegiline to methylphenidate for treatment of ADHD found no significant differences between the two medications, and that selegiline was well tolerated [61, 62]. When compared to placebo in a double-blind crossover study of pediatric ADHD and comorbid Tourette's syndrome, post hoc analyses revealed a substantial effect by selegiline in the group that received the active drug first in the crossover condition [63]. More recently, authors of a placebo-controlled RCT found that while selegiline did not specifically reduce symptoms of impulsivity, it was not associated with negative side effects, and may be a preferred treatment for individuals who present with the primarily inattentive subtype of ADHD [64]. Conversely, in a double-blind cross-over study, an alternate MAOI, tranylcypromine, was efficaciously indistinguishable from dextro amphetamine (a CNS stimulant) in the treatment of child and adolescent ADHD [65].

RCTs versus Naturalistic Studies

The "gold standard" of evidence-based medical research is the double-blind, randomized, placebo-controlled study (RCT) [66]. Participants either receive the intervention, substance or treatment in question, or no treatment or placebo, and neither researcher nor volunteer knows who belongs to which group. The defining feature of RCTs is the random assignment of participants to these conditions, and it is regarded as indispensable to ensure the observed effects can be attributed exclusively to the applied therapy (internal validity; [67]. RCTs are therefore intended to rule out bias and provide explicit evidence of a treatments efficacy [66]. The main controversy of RCTs is the concern over the external validity of RCTs: whether the results of RCTs are representative of clinical practice [67]. The strict control inherent in RCTs gives rise to idealized conditions, promoting the study of isolated disorders and restricted symptomology that rarely exists in real world clinical practice. How germane the results of RCTs are to everyday practice cannot be assessed without measurements of outcomes in the field [17] comorbidity, and response to pharmacotherapy in children and adolescents with obsessive-compulsive disorder (OCD.

In juxtaposition to RCTs, naturalistic studies are carried out under the natural conditions of clinical practice. Naturalistic studies are prospective "non-interventional" observational studies of phenomena or retrospective analyses of existing data from previously conducted studies, such as follow-up studies of previously treated participants or chart review data [68]. Naturalistic studies of antidepressants have been employed to study a broader range of clinically afflicted participants. Most RCTs have strict inclusion and exclusion criteria that limit participation based on comorbidities, illness severity, or medication history. Naturalistic studies, however, study antidepressant agents in the "real world" treatment of disorders without excluding patients suffering from suicidal ideation or behaviour or any co-morbidities, which so often occur in naturalistic samples. In this respect, naturalistic studies can provide more generalizable results in comparison to RCT efficacy trials [9]. Therefore, RCTs and naturalistic studies serve different purposes and provide answers to different domains of research questions. [68] reasons that naturalistic studies could be appreciated in conjunction with RCTs, as they can provide additional valuable knowledge to compliment the results of RCTs. Naturalistic studies provide the opportunity to observe clinician prescribing behaviours, undesirable medication effects and adherence under real world conditions, and the realistic course of treatment [68]. Long term naturalistic prospective studies in paediatric patients represent an important source of information for routine care regarding the effectiveness, safety, and tolerability of treatment over extended periods under routine clinical conditions [17] comorbidity, and response to pharmacotherapy in children and adolescents with obsessive-compulsive disorder (OCD.

Naturalistic Studies of Antidepressant Drug Treatment in Children and Adolescents

SSRIs

In an open, naturalistic study of 211 children and adolescents in Sweden, SSRIs were found to be the most prescribed antidepressant drug treatment, sertraline being the most common (67% of SSRIs). The indication for which antidepressant treatment is most commonly prescribed in the pediatric population was depression (69%), OCD second (14%), anxiety disorders (11%), dysthymic disorder (2%) and eating disorder (1%; [12] in terms of steady-state and trough values, in patients from Child and Adolescent Psychiatry centers in the midsouth-eastern part of Sweden, were evaluated, and the use of ATDs in this population were described. Patients to be prescribed an ATD were studied between 2002 and 2004. Two hundred eleven children, 64% girls and 36% boys (ages 8-20 years. A similar perspiration pattern was found in a study of antidepressant tolerability in anxious and depressed youth at high risk for bipolar disorder. SSRIs were also the most had been prescribed for 66% of these youths, 38% had taken bupropion, and 5% duloxetine

[69]. 57% of these high risk youth had an adverse reaction to antidepressant treatment that led to discontinuation, the most common cause being increased irritability, followed by aggression. Younger patients were more likely to experience antidepressant-induced adverse events and the authors observed trends toward higher irritability and motor hyperactivity in patients who subsequently developed adverse events with antidepressant treatment [69].

The most widely 'real world' studied SSRI in paediatric psychiatric populations is fluoxetine. In a naturalistic 1-year follow-up study of 87 children and adolescents who had participated in an 8-week RCT of fluoxetine for depression conducted by Emslie and colleagues (1998), symptom response to fluoxetine was superior to placebo. Of those treated with fluoxetine, 81% recovered within 12 months with an average time to recovery of over 2 months (69.4 days) and for those with recurrence, occurring at average 6 months (176.6 days) following recovery [20]. Similarly, in a naturalistic study on the efficacy and safety of fluoxetine in young patients (11-23 years), patients showed improvement in their symptomology over time, including suicidality, and adverse events of the naturalistic study were lower when compared to controlled trials [70]. In another naturalistic 1-year follow-up study, results showed that when combined with cognitive behavioural therapy (CBT), fluoxetine treatment reaches maximum benefit earlier (18 weeks) than either treatment alone (30 weeks for fluoxetine, 36 weeks for CBT), and that 9 months of treatment was superior to 12 weeks irrespective of treatment arm [71]. These results confirm those of a previous naturalistic study on combined fluoxetine and psychosocial therapy [72]. Most recently, fluoxetine was determined effective for the acute treatment of social anxiety disorder in children and adolescents, and it well tolerated except for mild and transient headaches and gastrointestinal side effects. Very few (5%) of the patients discontinued the fluoxetine because of side effects (increase in irritability; [73].

In another study on relation between dosage, serum concentration, and clinical outcome in children and adolescents treated with sertraline, no significant association between the serum concentration and the reported therapeutic response or the occurrence of side effects, however there was a trend that side effects occurred more frequently and with greater severity in adolescents than in children [74]. In a naturalistic study examining the effectiveness and safety of paroxetine for children and adolescents with panic disorder, the SSRI was well tolerated and effective for 83% of patients and there were no treatment interruptions due to side effects [75], replicating the results of Wagner and colleagues' RCT (77.6% response rate; 2004). However, in a naturalistic study assessing the long-term treatment of panic disorder with clonazepam (a benzodiazepine) or paroxetine, there was a significant advantage with clonazepam over paroxetine with respect to the frequency and nature of adverse events [76]. In an analysis of 23 cases of paediatric obsessive compulsive disorder treated with citalopram, over 75% showed a marked or moderate improvement in OCD symptoms [77], a response rate higher than those reported in RCTs (56.1%; [78], and any adverse effects were minor and transient.

NaSSAs

There were no available naturalistic studies assessing NaSSAs in child and adolescent depression. One naturalistic study of mirtazapine in pediatric populations was found for the treatment of associated symptoms of autism and other pervasive developmental disorders (PDDs). Overall, mirtazapine was well tolerated but showed only modest effectiveness (34.6%) for treating the associated symptoms of autistic disorder and other PDDs [79]. The minimal adverse events reported consisted of increased appetite, irritability, and transient sedation.

TCAs

The only naturalistic study on TCAs in child and adolescent psychiatry focused on the predictability and stability of desipramine concentrations in pediatric samples. Authors found wide between-patient variability in serum desipramine levels at the same dose, however future within-subject blood levels were highly predictable by knowing current levels, current dose, and the future dose [80] estimating the risk of developing potentially toxic DMI levels at a higher dose after a most recent level in a clinically acceptable range. METHOD: Subjects were 90 consecutive psychiatrically referred children and adolescents treated with DMI with at least two assays of serum DMI concentrations (462 pairs . No naturalistic studies were available for the efficacy and safety of other TCA agents in child and adolescent psychiatry.

Limitations and Issues in Naturalistic Studies

To date, greater focus has been paid to the methodological and ethical considerations of RCTs than on naturalistic studies [82]. Helmchem (2011) purposes this is because RCTs are interventional in nature and pose greater potential somatic and psychosomatic risks, whereas naturalistic studies are observational with an analytic focus. Generally, naturalistic trials pose no individual benefit to the participant, and therefore are assumed to have fewer or no risks [68]. It is important to appreciate, however, that in all classes of scientific study there are inherent risks, no matter how salient. The major methodological and ethical considerations of naturalistic studies are the method and content of informed consent, psychological burdens of questionnaires and/or interviews, psychological consequences of the observational procedures, and the confidentiality of recorded data. Two additional areas of great concern in naturalistic studies are the potential of stigmatization by case selection and dealing with incidental findings.

Most patients in naturalistic settings are not pharmacologically naïve and do not remain on the same antidepressant dosage for the duration of treatment, which may result in cross-tolerance or change side-effect reporting [83]. Therefore, while RCTs may be criticized over their external validity, a main argument against naturalistic studies regards threats to internal validity. However, according to [84], RCTs and naturalistic studies do not differ in their internal or external validity. The author purposes that in RCTs, laboratory hypotheses and laboratory modifications of therapy are tested, whereas in naturalistic studies, field hypotheses and field therapies are tested (2004). As such, RCTs should not

be considered to provide a higher level of evidence than naturalistic studies, but rather that each domain of research provides the necessary evidence for their domain of application. Nevertheless, the use of additional design elements can help minimize possible threats to internal validity of naturalistic studies. According to both [84] [68], a high-level prospective naturalistic study should use systematic and standardized observations at multiple time points and a schedule for data analysis determined prior to commencement. In addition, non-random comparison groups, matching or stratifying of groups, use of reliable and valid diagnostic procedures and outcome measures, pre- and post-assessments, and follow-up studies all contribute to a scientifically sound naturalistic study [84] that is, the structuralistic view of theories, the author shows that randomized controlled studies (RCTs.

Conclusion

The purpose of this report was to conduct review of antidepressant medications, their applications, and the controlled and naturalistic assessment to date in paediatric populations, in order to effectively inform a proposal for a realistic and comprehensive prospective naturalistic study of antidepressant medication in child and adolescent psychiatry. Antidepressant agents have successfully been applied in the treatment of many paediatric psychiatric disorders, such as depression, anxiety disorders, OCD, and ADHD, as demonstrated by RCTs. Of which the most evidence has been gathered on the antidepressant class SSRIs. However, there is little knowledge of the effectiveness of antidepressant treatments in paediatric psychiatry services in naturalistic "real world" settings [85] [12]. Given the wide-ranging application of antidepressants in everyday care, the efficacy rates in clinical trials may not be replicated in clinical practice. Therefore, it is imperative to conduct effectiveness studies of antidepressants in treatment-as-usual for children and adolescents, to complement RCTs. Further naturalistic studies are necessary to ensure that children are not exposed to unnecessary risk, and to determine the most appropriate agents and doses in children of different ages with different diagnoses [12] in terms of steady-state and trough values, in patients from Child and Adolescent Psychiatry centers in the midsouth-eastern part of Sweden, were evaluated, and the use of ATDs in this population were described. Patients to be prescribed an ATD were studied between 2002 and 2004. Two hundred eleven children, 64% girls and 36% boys (ages 8-20 years. Although there are inherent limitations of naturalistic studies, a number of strategies have been highlighted to bolster internal validity, such as non-random comparison groups and stratifying of groups. Given the paucity of naturalistic studies in diagnostically heterogeneous paediatric populations, the results of studies of this kind will help us better understand the efficacy, tolerability, and safety of antidepressant agents in children and adolescents.

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