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Paediatric antidepressants: Benefits and risks

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Abstract. The data supporting the use of "antidepressants" in children and adolescents is largely unavailable. Academic publications give a different picture as regards benefits and harms to publications from regulatory other sources. Despite disagreements about the data driving use of these medicines, in practice "antidepressants" may now be the most commonly used drugs by adolescent girls, and children's mental health services are attracting increasing attention.

This paper reviews the difficulties surrounding the data. It outlines a case for benefits (as well as risks) that would require physicians to exert a greater degree of professional autonomy than service managers might wish.

Keywords: Antidepressants, SSRIs, RCTs, anxiolytic, depression

1. Introduction

In 2016, Britain's Health Minister stated children's mental health services are the greatest failing of the National Health Service. Press coverage of his statement focussed on depression and noted that concerns were being raised even though despite substantial increases in funding children were attempting suicide while on waiting lists [2].

The selective serotonin reuptake inhibitors (SSRIs) were developed by Carlsson to allow the differences between catecholamine (energy enhancing) and serotonergic (cognitive/ anxiolytic) therapeutic principle to be distinguished in a way that was not possible with tricyclic antidepressants. At the launch of the SSRIs in the 1990s, there had been 15 randomized controlled trials (RCTs) of tricyclic and related antidepressants in children, all negative [12].

In 1997, an NIMH funded trial of fluoxetine in adolescent depression reported a benefit [3], as did a second RCT [4]. These trials and a trial in OCD led regulators to approve claims fluoxetine could benefit adolescent depression and OCD. Subsequently trials for paroxetine [14] and sertraline [23], and citalopram reported benefits [24]. Sertraline was also approved for OCD.

In 2004, doubts were raised about the benefits and safety of these drugs for children. The United States Food and Drug Administration (FDA) identified 15 paediatric antidepressant trials and designated the two fluoxetine studies and one citalopram study as positive and all paroxetine, sertraline, venlafaxine, nefazodone and mirtazapine trials as negative.

The FDA analysis of these trials reported a doubling of suicidal events (absolute increase of 1%) on active treatment, and this led to a Black Box warning, as much perhaps because of the background lack of efficacy as for the data on suicidal events.

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Table 1
Studies done from 1990 to 2005

Study	Primary Outcome	Source	Suicidal	Numbers
Paroxetine				
329	N	Le Noury et al.	XS	275
377	N	Laughren	XS	276
701	N	Mosholder	XS	206
511	N	Braconnier et al.	XS	125
Sertraline				
1001	N	Laughren	XS	373
1017	N	Laughren	XS	(1001 and 1017)
Fluoxetine				
1990	N	Simeon et al.	XS	40
X065	N	Mosholder	XS	96
HJCE	N	Mosholder	XS	219
HCCJ	N	Mosholder	XS	40
TADS	N	March et al.	XS (34v3)	439
Venlafaxine				
Mandoki	N	Mandoki et al.	XS	40
382	N	Laughren	XS	165
394	N	Laughren	XS	196
Citalopram				
94404	N	Laughren	XS	233
Cit 18	N	Jureidini et al.	?	174
Sct 15	N	CSR	?	266
Nefazodone				
141	N	Laughren	XS	190
187	N	Laughren	XS	278
Mirtazapine				
0045	N	Laughren	XS	258

Legend: N = negative; OL = open label; XS = excess.

A recent analysis [17] of paediatric depressive and anxiety disorder RCTs, calculating effect sizes using scores on rating scales with continuous variables such as the Childrens' Depression Rating Scale (CDRS), or CYBOCS, suggested there was evidence of a minor benefit in depressive and anxiety disorders.

2. Trial analysis

We have categorised all depression trials undertaken as positive or negative on the basis of the findings on the a priori declared primary outcomes using Clinical Study Reports (CSRs), an FDA review of the issue in 2004 [15], FDA reviews of the fluoxetine paediatric application [21], and company reports on clinicaltrials.gov.

Taking this approach, all 20 trials conducted in children with depressive disorders between 1990 and 2006, almost 4000 children, were negative (see Table 1).

The primary outcomes for the two fluoxetine trials commonly cited as positive, which provided the basis for approval of the drug, were negative [21]. In seven trials in which fluoxetine has been compared

to placebo, alone or in a design with duloxetine or venlafaxine, it has been negative on the primary outcome.

The citalopram trial claimed as positive [24] is not positive on its primary outcome if the results are analysed per protocol [13]. A recent (es)-citalopram study report claims a benefit on the primary outcome measure on the basis of a 3.3 point difference between citalopram and placebo in the reduction from their respective baselines [5]. This is not a clinically meaningful difference in a scale with a range of 96 points.

The data from these sources make it clear that there was an excess of suicidality on active treatment in all trials.

The present authors reanalysed Study 329 in which paroxetine was claimed to be effective and safe [14] and found that no method of analysis produced a positive result on the primary outcome [16]. We also found more than double the number of suicidal events compared with the originally reported claims.

There are no grounds for thinking other paediatric antidepressant studies are exempt from the findings and lessons from the restoration of Study 329 and the re-examination of CIT-18, namely that when analysed strictly per protocol the basis for efficacy in depressive disorders claims for benefits shrink and the number of recorded harms grows.

Since 2006 there have been a further 15 depression studies involving over 6000 patients (Table 2). These have mainly involved duloxetine, (des)-venlafaxine, (levo-) milnacipran and vortioxetine, but have also included one (es)-citalopram and one paroxetine study. When considered in terms of primary outcome measures these depression studies have also been negative, with the possible exception of the (es)-citalopram study mentioned above.

While the depression trials were ongoing, a series of trials of the same drugs in OCD and other anxiety states were undertaken. A proportion of these trials appear positive on their primary outcome measures. Some studies with negative outcomes on the primary outcome measure remain unpublished. There is an excess of suicidal events on active treatment in these trials also.

3. Use of antidepressants

The state of the evidence for the use of antidepressants in paediatric depression as of 2004 illustrates the greatest known divide between a set of Open Label studies claiming benefits (N = 70) and RCTs pointing consistently in the opposite direction. Given the RCT findings, one might have expected the then growing use of antidepressants in minors to have declined. But in the decade since 2004, while establishing the details of use is difficult as prescription data is only available on a commercial basis, it appears antidepressants are now among the most commonly prescribed drugs in adolescents, particularly in girls. There has been a 100-fold increase in Britain, and a recent CDC publication places the use of antidepressants among American adolescents potentially at 13% [20].

This increase in use likely stems from the positive view of efficacy in the published literature, along with an absence of harms. Even hints of efficacy will lead to prescriptions, when despite warnings in this age group, the academic literature makes little reference to harms or is dismissive of this possibility [17].

For instance, March and colleagues in the 2004 TADS study concluded: “The combination of fluoxetine with CBT offered the most favorable trade-off between benefit and risk for adolescents with major depressive disorder”. The TADS study gave rise to seven publications in major journals, none of which drew attention to the occurrence of 34 suicidal events on fluoxetine compared to 3 on placebo [11].

Table 2
Studies after 2006

STUDY	Primary Outcome	Source	SUICIDAL	Numbers
Paroxetine				
2487	N	ClinTrials.gov	?	56
Fluoxetine				
Duloxetine trials	N	ClinTrials.gov	XS	
Venlafaxine				
1012	N	ClinTrials.gov	XS	40
1014	N	ClinTrials.gov	XS	340
1032	N	ClinTrials.gov	XS	363
Tordia	N		XS	334
Citalopram				
Sct 32	N?	CSR	XS	316
Duloxetine				
11664	OL	ClinTrials.gov	XS	72
6223	N	ClinTrials.gov	XS	337
7109	N	ClinTrials.gov	XS	463
L-Milnacipran				
Lev-MD-11	Not Reported	ClinTrials.gov		660
Vortioxetine				
12712	OL	ClinTrials.gov		1068
12709	Not Reported	ClinTrials.gov		750
12710	Not Reported	ClinTrials.gov		750
Vilazodone				
MD-22	Not Reported	ClinTrials.gov		470
MD-21	N	ClinTrials.gov	XS	529

Legend: N = negative; OL = open label; XS = excess.

Challenge-dechallenge-rechallenge reports from the early 1990s in children as well as adults including a completed suicide in a child with OCD established conclusively that these drugs can cause suicide and the clinical trial data shows more children progress to a suicidal event than are prevented from a suicidal event in these 6–8 week trials.

There are other problems. All SSRIs affect QT intervals and are increasingly combined with other psychotropic agents which have effects on QT intervals [6].

In close to 100% of individuals who take an SSRI there is an immediate genital numbing. In a proportion of cases this endures semi-permanently after treatment stops, for which at present we have no remedies [10].

We do not know what proportion of adolescents who take antidepressants are unable to get off them, but current data suggests over 80% of antidepressant takers of all ages have been on treatment for more than a year. A significant proportion of these are likely to be continuing treatment because of difficulties in stopping.

Dependence is problematic in adolescents as SSRIs inhibit growth velocity, and cause weight gain, which if effectively permanent because of dependence may be problematic for self-image, in addition to increasing the risk of diabetes and other disorders.

Women enter the child-bearing years in adolescence. There is a significant evidence that SSRIs cause birth defects [7] and Autistic Spectrum Disorders [8] in addition to triggering miscarriages which are a risk factor for future mental health problems.

If primary care treatment goes wrong, subjects presenting to secondary services with complex pictures involving suicidality or disinhibition or antidepressant induced alcoholism, may end up diagnosed as bipolar and given inappropriate treatments often concomitantly.

Statements to the effect that the risk-benefit ratio of treatment remains favourable on the basis of clinical trials that last for only 6–8 weeks and fail to record the adverse effects of treatment properly, and where the data is inaccessible are problematic, particularly in the absence of evidence of efficacy. The notion of a risk benefit ratio for any drug is recent. Before 1990 the medical brief was to balance the harms from a drug against the harms of the condition.

4. Deriving a benefit

There is another way to think about the clinical utility of these drugs. This lies in a return to the thinking that gave rise to SSRIs, which was an effort to make a specific therapeutic effect more visible. This therapeutic principle appears to be a form of anxiolysis referred to by many on treatment as emotional numbing, and at one point marketed as a serenic effect. This effect can be distinguished from the effects of antipsychotics, benzodiazepines and beta-blockers, which might also be termed anxiolytics.

It would seem highly likely that in appropriately designed trials, perhaps lasting no more than a week, there would be a clear and relatively immediate distinction between SSRIs and placebo on an outcome measure like a serenic effect.

No such trials have been done but recently Eriksson and colleagues have meta-analysed SSRI trials focusing on the depression item from the Hamilton Depression Rating Scale, on which they claim a significant change on medication compared to placebo [9].

This finding fits the view offered here in that one would expect an anxiolytic treatment to produce a more distinct difference on an item of the HDRS such as the depression or anxiety item than it does on the overall clinical condition. The view is also supported by the evidence these drugs produce a more distinct benefit in OCD and other anxiety disorders that in paediatric "depressive disorders".

While there would be problems to overcome in acknowledging that a serenic effect is the therapeutic target of serotonin reuptake inhibitors, there is also much to gain. Designating a serenic effect as the primary outcome not just of trials but of therapy would help make clinical practice more rational. A patient, told that this is the effect desired, could contribute to care by reporting whether the treatment was having this effect. Where the desired effect is not happening, there would be an earlier opportunity to switch to a different therapeutic principle, reducing the likelihood of adverse reactions linked to the agitating effects these drugs can have in the short term and weight gain and other effects in the longer run.

If producing a serenic effect was the primary outcome of trials, the differences between the drugs and placebo would likely make claims that the effect of these drugs are all in the mind or the drugs don't work redundant. The key point for debate and research instead would centre on establishing when it is reasonable to deploy such a therapeutic principle – in which age groups and for how long. The key point in clinical practice would centre on professional discretion rather than guideline or even indication mandated treatment approaches.

Conflict of interest

DH and JJ have been expert witnesses for plaintiffs in legal cases involving SSRI harms. JLN has no conflicting interests to declare.There is no external funding for this article from any source.

Statement re access

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