

THE SSRI DEBACLE

CURRENT SITUATION AND PRACTICAL RECOMMENDATIONS TO CLINICIANS TREATING DEPRESSED CHILDREN AND ADOLESCENTS IN EUROPE

Prof. Dr. med. J. M. Fegert

Universitätsklinikum Ulm
Klinik für Kinder- und Jugendpsychiatrie/Psychotherapie
Steinhövelstraße 5
D-89075 Ulm
Tel.: 0049 7 31 5 00 - 3 35 44 / 45
Fax: 0049 7 31 5 00 - 3 35 46
E-Mail: joerg.fegert@medizin.uni-ulm.de

Abstract

The current debate on SSRI use is based on a reanalysis of all controlled trials involving children and adolescents done by the FDA. Based on these data the FDA decided to issue a black box warning, concerning all antidepressant treatments for children and adolescents (SSRI, tricyclics, NARI, MAO inhibitors and other medications). The British agency MHRA issued a contraindication concerning all SSRIs except fluoxetine. Most of the other European agencies still have not published a final statement on the issue.

The current paper revises the development of that crisis and gives some interpretation about the risk benefit relation of antidepressant treatments under these conditions. Clinical recommendations for continuation and initiation of treatment are given.

Keywords: SSRI, suicidal behaviour, depression

1. Introduction

Since the first airing of the BBC Film “the secret of seroxat” on 13th of October 2002 in Europe as well as in the US an increasing amount of publications and contradictory information causes a vivid debate about risks and benefits of SSRI treatment in depressed youth. Parents and depressed children are alarmed and their spontaneous reactions to reports in the media are becoming more and more a further risk in the treatment of depression in child and adolescent psychiatry. The general acceptance of the use of psychotropic agents in the treatment of children and adolescents that had grown in the last decade [14] is again declining. There is an ongoing discussion on publication bias and the need of transparent information of the public and the prescribers and patients. The fact that the new European database on clinical trials (EUDRACT) will not be publicly accessible raises critiques on the relative importance of transparency and treatment safety on the one hand and patent holder propriety issues on the other hand. Well founded critical reviews [1] as well as conspiracy theories on the cooperation of doctors and industry spread out as do personal reports of families who lost a child under SSRI treatment (and many other factors not taken into consideration). In many places clinicians nowadays avoid the off label prescription of SSRIs and return to tricyclics whereas in some countries (e.g. germany) a majority of physicians never gave up this habit reinforced by the labelling situation (due to historical labelling procedures some tricyclics are labelled in some European countries for the use in childhood depression – although there is no prove of their efficacy for this indication in this age group in a clinical trial or a meta – analysis [7]. If clinicians still prescribe SSRIs some tend to use low dosages to avoid harm ignoring the fact that children and adolescents generally metabolize antidepressants more rapidly than adults [2], [6]. Some refrain from prescribing SSRIs even in

situations where we can find promising results (PTSD and anxiety) and established indications with childhood labelling of different substances in different countries as in obsessive-compulsive disorder. Some adult psychiatrists get worried about the fact that their patients as well are now questioning their treatment [10]. The FDA adds to this confusion by publicly announcing in a mass media interview the reanalysis of a pool of adult data which covers 234 clinical trials involving about 40 000 adults. At the end of 2004 SSRIs except fluoxetine are contraindicated in Great Britain for the use in children and adolescents, while as the FDA in October issued a black box warning concerning the use of all antidepressants (SSRIs, NARIs, MAOIs TCAs and others) in children and adolescents.

Table 1: Studies on TCAs in childhood depression

<u>STUDY</u>	<u>N</u>	<u>AGES</u>	<u>DRUG</u>	<u>WKS</u>	<u>DRG RES</u>	<u>PLB RES</u>
Kramer 1981	20	A	amitriptyline	6	80%	60%
Kashani 1984	9	C	amitriptyline	4	67%	56%
Puig- Antich 1987	38	C	imipramine	5	56%	68%
Geller 1989	50	C	nortriptyline	8	31%	17%
Geller 1990	35	A	nortriptyline	8	8%	21%
Boulos 1991	30	A	desipramine	6	50%	33%
Kutcher 1994	60	A	desipramine	6	48%	35%
Kye 1996	31	A	amitriptyline	8	56%	15%

The objective of this article is to summarize the facts until October 2004 and to give some clinical and political advice in the current situation in Europe given a heterogeneous regulatory and pharmaco - epidemiological prescription situation.

2. Development of the SSRI controversy

In January 2003 the US regulatory agency FDA approved fluoxetine for paediatric use in MDD and OCD. The British agency MHRA issued a warning about paroxetine in children and adolescents based on a confidential report concerning 3 studies with paroxetine including 748 children and adolescents. Events possibly related to suicide occurred in 3,7% in the treatment group and 2,5% in the placebo group . That means there was a non significant ($p = 0.50$) increase of relative risk (1.5 95%CI: 0.6, 3.4). Including the 30 day follow up period event rates in the paroxetine group raised to 5,3% vs. 2,8% the increase of relative risk still remained non significant ($p = 0.12$). Adding the data from the other trials including children with OCD possibly suicide related events went down to 2,4% in the on therapy group vs. 1.1% in the placebo condition ($p = 0.07$) and to 3,4% vs.1,2% if the 30 day follow-up period was included ($p = 0.01$). The authors of the report conclude: *“This means that any possibility of a protective effect is minimal, but the excess risk could be over 5-fold”*

From this time on the public discussion mainly focussed on risks in treatment with SSRIs avoiding the issue of poor treatment outcome and lack of prove of efficacy. Clinicians in contrary stressed the clinical effectiveness and importance of SSRIs based on their personal impressions. Some epidemiologists started to discuss the development of suicide rates since the

introduction of these medications in search of a proof of their general benefit [12].

In July 2003 FDA addressed a request for paediatric suicidality summary data to patent holders of 8 other antidepressant products. Wagner et al. published their study on the efficacy of sertraline in August 2003. At the same time Wyeth issued a warning to doctors concerning venlafaxine and proactively got a label upgrade in the US while MHRA issued a warning on venlafaxine. The FDA sought outside review to reclassify probably suicide related events at Columbia University.

At the end of 2003 the British agency's warning regarding antidepressants was extended to a contraindication of all SSRIs except fluoxetine, followed by a FDA general warning in March 2004 after a first FDA public hearing in February and a warning by health Canada.

(<http://www.fda.gov/cder/drug/antidepressants/default.htm>.)

Whittington et al. [16] published in the lancet the first systematic review of published vs. unpublished data and conclude: *“Data for two published trials suggest that fluoxetine has a favourable risk-benefit profile, and unpublished data lend support to this finding . Published results from one trial of paroxetine and two trials of sertraline suggest equivocal or weak risk-benefit profiles. However in both cases, addition of unpublished data indicates that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine show unfavourable risk – benefit profiles.”*

Different papers claim that we need full access to data of positive and negative trials [3], [4], [8], [17]. In June 2004 New York state attorney Eliot Spitzer filed suit charging UK based drug company glaxo smith Kline with “repeated and persistent fraud”

alleging that it only published positive results of its paroxetine trials. In summer 2004 this legal affair was settled against the payment of more than 2 Million Dollars. Since the FDA hearing there had been rumours that the FDA had suppressed a critical report by FDA's child psychiatrist Andy Mosholder stating that there is a two fold risk of suicide related behaviour in the use of SSRIs compared to placebo. US Congress started an investigation against FDA . Finally in August 2004 BmJ and New York Times got access to Dr. Mosholders 33 page memorandum and FDA launched a criminal investigation to find out who leaked the report. The results of the reclassification analysis by the Columbia team were put on the internet by the FDA in August. Mid August the TADS study (Treatment of adolescents with Depression Study – a randomized controlled clinical trial done by a research team and publicly funded) was published in JAMA [13] [15]. This was the first study comparing medication and psychotherapy and the combination of both to placebo. The combination of fluoxetine with CBT offered the most favourable statistically significant results over placebo and showed a response rate of 71%. Fluoxetine alone (response rate 60.6%) was statistically superior to CBT alone (43%, the response rate of placebo being 34,8 %). With respect to suicide risk the authors found that clinically relevant suicidal thinking was present in 29% of the sample at baseline and improved significantly in all 4 treatment groups, the combination therapy showing the greatest reduction. In that sample of 439 youths suffering from moderate to moderately severe MDD (CDRS-R t score average was 76 at the beginning of treatment, current major depressive episode duration median was 48 weeks) seven patients (1,6%) attempted suicide. Like in the other studies there was no completed suicide. CBT had a specific beneficial effect on suicidal thinking.

The TADS fluoxetine and Placebo data have been included in the FDA risk analysis and presented in September 2004 at a second public hearing.

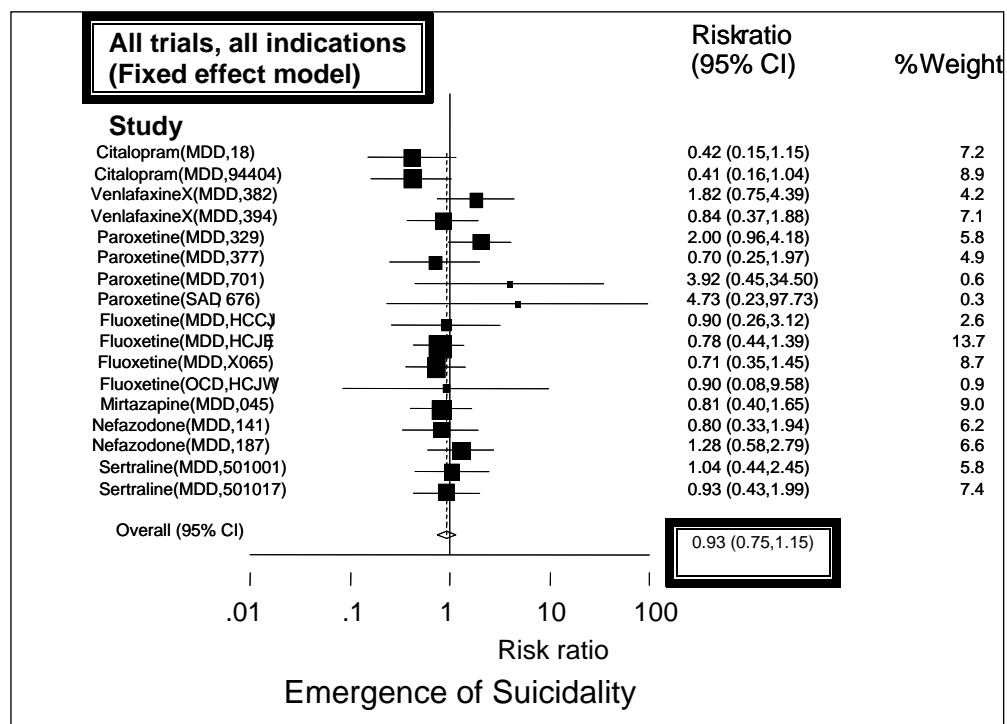


Table 2: Emergence of Suicidality source modified from FDA, T. Hammad Presentation 13.-14. September 2004

The members of the two advisory committees concerned (psychopharmacologic drugs and paediatric advisory committee) concluded that the finding of an increased risk of suicidality in clinical trials was a group effect and recommended that any warning related to an increased risk should be applied to all antidepressant drugs studied or not and a patient information should be provided to children and their caregivers with every prescription. They reached a split decision (15 yes 8 no) recommending a so called black box warning but were unanimous that these drugs should not be contraindicated because the access to these therapies was important for those who could benefit. The controversy on the pros and cons of a black box warning was made public by the N ENG J Med asking to committee members to comment [11], [10], [2].

Finally the FDA on Friday October 15 2004 launched a strategy including a black box warning to strengthen safeguards for children and adolescents treated with antidepressant medications.

Suicidality in Children and Adolescents

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Until now European agencies (except the British contraindication) are still making up their minds and confront clinicians and the media with some sort of “selective mutism”. On the one hand this causes a lot of confusion in patients families and doctors on the other hand this gives us a chance to formulate some applicable principles as researchers and clinicians¹.

¹ The leaders of the research group (Findling) and the pediatric psychopharm initiative (Greenhill) of the AACAP asked the author to comment on the consequences of these analysis in Europe and to give clinical treatment recommendations based on a former statement of the german professionals society DGKJP(Fegert & Herpertz-Dahlmann 2004) at the town meeting at 51st annual convention of the AACAP. The recommendations in this article are based on this presentation. They are the personal opinion of the author and not an official expression in one of his functions as head of

3. Clinical recommendations for the treatment of depressed children and adolescents

Clinical recommendations have to be based on a pharmacoepidemiological analysis of prescribing patterns and treatment resources in different countries because access to care and the possibilities of surveillance of side effects are different in most European countries. In some countries a major part of depressed patients is seen by general practitioners or paediatricians versus in some other countries child psychiatry is sufficiently developed and there are sufficient treatment facilities for inpatient and outpatient treatment of childhood depression. Reactions of national agencies should take in account this specific national situation and specific national prescribing patterns. In the aim to get some orientation about these differences and the different conclusions we have to draw from the specific situation a pharmacoepidemiological research group led by Julie Zito² presented the comparison of SSRI use in Dutch, German and the United States youth at the International Society of Pharmacoepidemiology in Bordeaux and at the IACAPAP Meeting in Berlin, both in August 2004. The analysis was based on a Dutch cohort of 72.570 enrollees, a German cohort of 480.680 enrollees and Mid-Atlantic state S-CHIP cohort of 125.157 enrollees. We found a wide disparity across systems. Antidepressant prescriptions had been 15 times greater in the US middleclass sample than in the German and 3 times greater than in the Dutch cohort despite a similar theoretical approach to child psy-

the commission on developmental psychopharmacology of the DGKJP or as a member of the commission at the German regulatory agency.

² J. M Zito, PhD, University of Maryland, School of Pharmacy and School of Medicine, L. van den Berg, PhD, H. Tobi, PhD, University of Groningen, Netherlands, K. Jahnsen, PhD, University of Bremen, J. F. Gardener, University of Maryland, School of Pharmacy and J. M. Fegert, University of Ulm, Germany

chiatry. Older Girls where most prominent in Dutch and German prescriptions whereas 5 – 14 year olds where prominent in the US cohort. Subclass analysis showed that tricyclic antidepressants are still the most prescribed antidepressant drugs among the youth in Germany while as in the US and Dutch population SSRI had been the most commonly prescribed drugs. Tab. 3 gives an overview of antidepressant prescriptions, paroxetine (27% Netherlands, 24% US) accounted for a quarter of all antidepressant prescriptions in the Dutch and US cohort while as imipramine and amitriptyline represented 45% of the prescriptions in Germany. [5]

3: Leading antidepressant as a proportion of all ATD users.
Source Fegert et al. 2004

Leading antidepressants as a proportion of all ATD users						
	Dutch n=390		German *) n=522		US-SCHIP n=2067	
		%		%		%
Drug 1	Paroxetine	27	Imipramine	32	Paroxetine	24
Drug 2	Amitriptyline	16	Amitriptyline	13	Sertraline	23
Drug 3	Fluoxetine	14	Opipramol	12	Fluoxetine	18
Drug 4	Imipramine	14	Doxepine	11	Bupropion	18
Drug 5	Fluvoxamine	9	Fluoxetine	7	Trazodone	7
> 1 drug		5.9%		5.4%		21.3%

*) No herbal medicines included

Fluoxetine prescriptions ranked at a middle level of 7% in Germany, 14% in the Netherlands and 18% in the US population. Co medication was common in the American population (21,3%) while as in the Dutch and German cohort the rates where much lower (5,9%; 5,4%). Herbal medicines like Hypericum (St. John's Wort) had not been included in this comparison but are according to another study in a German sample [9] the predominant drug prescribed for childhood and adolescent depression in Ger-

many. The data show that the prescriptions of paroxetine or venlafaxine might be an important health issue in US-populations and in the Netherlands or the U.K. but aren't such an issue in Germany where still ineffective medications for the treatment of depression like TCAs with a high risk profile are widely prescribed. In the following recommendations I tried to take in consideration this heterogeneous situation in different European countries.

3.1. Treatment recommendations for child and adolescent depression

With respect to safety and efficacy SSRIs are the best studied medications in the treatment of childhood depression. TCAs are not effective in the treatment of childhood depression. Herbal medicines (e.g. hypericum) might be effective in mild childhood depression. In the current situation we have to distinguish two different situations, the continuation of an ongoing treatment and the initiation of treatment in new patients.

3.1.1. Continuation

If the clinical response to the prescribed drug was positive, doctors should inform patients and parents about the ongoing discussions and give them general information about the increased risk like in the black box warning of the FDA and of the need to monitor those patients and keep in contact with the prescribing physician. It is also very much important to warn parents and patients that a sudden withdrawal of these substances constitutes a major risk for the patients. If the clinical response on sufficient dosing was negative or insufficient the same general information should be given and the second SSRI and/or psychotherapy should be tried out next. The TADS study [13] shows that cognitive behaviour therapy reduces the risk of suicidal

ideation and has a significant treatment effect. Nevertheless in many countries in Europe there is a lack of access to well trained therapists who are in the same time used to combination treatments of medication and psychotherapy.

Important factors in reducing suicidal ideation with cognitive behaviour therapy might be the therapeutic relationship and psychoeducational elements that could be applied by every child psychiatrist.

3.1.2. Starting new treatments

It is difficult to give general recommendations with respect to treatment initiation because the individual situation of a family and the possibilities of parental supervision at home have to be taken into account. Given the fact that only fluoxetine showed positive treatment effects over placebo in every clinical trial done by industry and in the TADS study I would recommend to start new treatments with fluoxetine beginning like in the TADS study at a starting dose of 10 mg daily increased to 20 mg daily at week one and if necessary to a maximum of 40 mg daily by week eight, if the clinician diagnosed a moderate or severe episode of childhood depression. In light or moderate episodes psychoeducation and psychotherapy alone seems to be an adequate response. In the moderate and severe cases medication and a psychotherapeutic intervention should be combined if possible the ideal combination seems to be cognitive behaviour therapy and fluoxetine medication done by the same experienced child psychiatrist, this assures regular follow up of medication and current psychopathology. Before starting treatment patients should be informed about the relative risks and advantages of treatments and patients and parents should be informed about the risk of non treated childhood depression. If there is an urgent need of permanent supervision due to a high

suicidality of the patient, parents and patient should be encouraged to consent in inpatient treatment. If there is no consent but the psychiatrist sees a considerable risk lifesaving interventions should be law enforced in the best interest of the child according to national laws and regulations. In all clinical trials patients with real suicidality at the beginning and a high risk for a suicide had been excluded. An ongoing study at NIMH will inform us in the next years about empirical results in that clinical high risk population. It is difficult to apply the results of clinical trials generally in outpatients with moderate depression to this group of high risk patients with multiple co morbidities. All patients and parents should be informed about possible side effects and the need of parental supervision, a sufficient frequency of appointments and the possibility of phone contacts if there are treatment related side-effects or problems. But at the same time parents should be assured that a 100% control and supervision is never possible nor in a private home neither in a hospital. Depression and suicidality are linked. It is important to explain the results of the FDA review of the current studies to patients and parents in the way they can understand so that they can make up their own treatment decisions together with a physician. FDA analysis found that there is a two percent increase of suicidal ideation and/or self harm behaviour over the base rate created by depression itself. That means that among 100 patients with mild to moderate mood disorders treated with a SSRI one will expect three children and adolescents with increased suicidal ideation and/or self harming behaviour. One of those patients will statistically have experiences with symptom increase as part of the underlying mood disorder while two have increased ideation or self harming behaviour due to the medication. Given the response rates in the TADS study [13] (over 60% in the fluoxetine treatment group and about a third in the placebo group) one could conclude out of three treated patients one will have an insufficient response to fluoxetine, one will have his response

perhaps due to placebo and another one will have a real positive response to fluoxetine. This means that in that population of mild and moderately depressed children and adolescents a doctor would need to treat at least three patients to see a response to fluoxetine versus treating over 50 patients to see evidence of the medication causing an increase in suicidal ideation or self harm. After a long discussion in the AACAP workgroup on research and in the Paediatric Psychopharm Initiative the members of these groups find this risk benefit ratio for the treatment of paediatric depression acceptable. If there is no sufficient response after 10 weeks of treatment or if there is a worsening or emergent suicidality the SSRI dose should be tapered, any abrupt stoppage should be avoided (particularly in other SSRIs than fluoxetine with a different pharmacokinetic profile). If there is no sufficient response, another SSRI should be tried out and psychotherapy should be continued. Based on the overview of studies sertraline (especially in adolescents) and citalopram/escitalopram or another SSRI could be an alternative. Given the published warnings, paroxetine and venlafaxine usually should not be considered as a second line alternative. As long as there is no European labelling for fluoxetine as an indicated treatment of childhood depression parents have to be informed about the fact of off-label use of this substance and why we use this substance among the other non labelled and perhaps in some countries some older labelled but not effective and potentially harmful substances.

4. Political consequences

The discussion on contraindication, black box warning, different warnings, prescription restrictions, has caused a lot of political side effects and has confused many patients, parents and doctors. There is a small risk signal and there is an unclear benefit

situation in the treatment of depression with most of the known SSRIs except fluoxetine. There has been no pooling of efficacy data with the same methods at the FDA so we are only informed of the risk of the substance class but we don't know whether there is an overall positive trend on efficacy. We have only little information on an age specific response rate indicating that there might be a better response in adolescents than in smaller children. Many patients had been alarmed about these warnings and didn't understand the notion of a small risk signal. So sudden withdrawal from a clinically effective medication might be a high risk associated with this information situation.

The fact of non transparency in research results caused a major credibility problem of doctors and industry so that the European professional societies need to develop a strategy of transparency to make sure that usual cooperation in the benefit of children and adolescents will continue. As in the United States it will be important in the future in Europe to have other sponsors of clinical research than industry. Combined trials with psychotherapy or psychosocial intervention and medication or trials with psychotherapy alone will never be sponsored by the industry [14]. We need a better understanding of the interface between publicly founded and industry founded research and better opportunities for integration and collaboration in paediatric psychopharmacology and treatment research. According to European regulations and national law in many European countries, group benefit is the only ethical principal that legitimizes clinical trials in children. Therefore data have to be made fully available to the public. Child psychiatrists should not sign trial contracts with an absolute or relative veto right to publication by the sponsor. More research on age specific long-term effectiveness and long-term safety of psychopharmacological treatments in children and adolescents is needed. We need better information of patients and parents of general practitioners, paediatricians and

specialists and the media. European professional societies should prepare special internet pages like the facts for families of the American Academy as a reaction to the ongoing situation.

5. Conclusion

The SSRI problem should not be only discussed as a risk situation but in every single case the risk benefit ratio counts. The overall impact of the illness (mild-moderate depression vs. moderate to severe depression with comorbidities) on the patients and families every day life has to be taken into consideration. The possible benefit of SSRI use in the treatment of OCD, anxiety or PTSD is or might be much higher than in the treatment of depression whereas suicidal ideation and/or self harm occurred with a lower frequency in the accessible clinical trials even though there had been also a certain increase in the treated groups and only the pooling of all data including trials on other indications than depression gave enough statistical power to describe the safety signal on SSRIs. Nevertheless a clinical decision has always to be based on the potential benefits as well as on the known risk. Therefore the minor safety issue on suicidal thoughts in children and adolescents with OCD is acceptable with respect to the relatively high effect sizes of SSRIs in the treatment of childhood OCD. Child and adolescent psychiatrists and psychotherapists have to inform patients, parents and the public about these basic principals of decision making in the treatment of children and adolescents.

There are no simple answers to complex situations. Banning a group of medications involves a higher risk for patients and doctors and brings us back to a situation that we had known in the 80th and the early 90th of the last century in most of the countries in Europe, where long-term non evidence based treatments or no sufficient access to treatment where the rule for children with

need of child psychiatric interventions. The SSRI crisis dramatically points out that we don't need more ideological controversies and conspiracy theories on child psychopharm but that we need more evidence and more and better research to the benefit of children in order to have balanced treatment strategies founded on sufficient scientific evidence base.

6. Literature

1. Angell M (2004) *The Truth About the Drug Companies*. Random House, New York
2. Brent DA (2004) Antidepressants and Paediatric Depression - The Risk of Doing Nothing. *The New England Journal of Medicine*. 351:1598-1601
3. Fegert JM (2004) Depressionsbehandlung mit SSRI in der Kinder- und Jugendpsychiatrie - Ein Forschungs- oder ein Informationsdebakel? *Nervenheilkunde* 23: 60-64
4. Fegert JM, Herpertz-Dahlmann B (2004) Editorial. Zum Einsatz von selektiven Serotoninwiederaufnahmehemmern (SSRI) bei depressiven Kindern und Jugendlichen. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie* 32:74 - 75
5. Fegert JM, Jahnsen K, de Jong-van den Berg LTW, Zito JM (2004) SSRI use in children and adolescents in Europe and the United States: Cause of concern? In: Remschmidt H, Myron B (eds) *Book of Abstracts of the 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP)*, 22-26 August 2004, Berlin, Germany. Steinkopff, Darmstadt, p 74
6. Findling RL (2004) The Relevance of Pharmacokinetic Studies of Antidepressants. In: Remschmidt H, Myron B (eds) *Book of Abstracts of the 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP)*, 22-26 August 2004, Berlin, Germany. Steinkopff, Darmstadt, p 75
7. Greenhill L, Waslick B (2004) Selective Serotonin Reuptake inhibitors for the treatment of depression in 4.100 Children and Adolescents. In: Remschmidt H, Myron B (eds) *Book of Abstracts of the 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP)*, 22-26 August 2004, Berlin, Germany. Steinkopff, Darmstadt, p 74 - 75
8. Herpertz-Dahlmann B, Fegert JM (2004) Zur Problematik der Gabe von selektiven Serotoninwiederaufnahmehemmern (SSRI) bei depressiven Kindern und Jugendlichen. *Nervenarzt* 9:908 - 910

9. Kölch M, Bücheler R, Gleiter CH, Fegert JM (2004) Is St. John's Wort an evidence based treatment-alternative for depressed Minors? Facts and prescribing trends in Germany. In: Remschmidt H, Myron B (eds) Book of Abstracts of the 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), 22-26 August 2004, Berlin, Germany. Steinkopff, Darmstadt, p 347
10. Möller H-J (2004) SSRI zur Recht unter Anklage. *Psychopharmakotherapie* 3:69-70
11. Newmann TB (2004) A Black-Box Warning for Antidepressants in Children? *The New England Journal of Medicine* 351:1595-1598
12. Olfson M, Marcus SC, Greenberg T (2003) Relationship between antidepressant medication treatment and suicide in adolescents. *Archives of General Psychiatry* 60:978-982
13. The TADS Team (2004) The Treatment for Adolescents with Depression Study (TADS): Short-Term Effectiveness and Safety Outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry*. 7:807-820
14. Vitiello B, Heiligenstein JH, Riddle MA, Greenhill LL, Fegert JM (2004) The interface between publicly funded and industry-funded research in paediatric psychopharmacology: Opportunities for integration and collaboration. *Biological Psychiatry* 56:3-9
15. Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS, Childress A, Donnelly C, Deas D (2003) Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder. *Journal of the American Academy* 290:1033 - 1041
16. Whittington CJ, Kendall T, Fonagy P, Cotrell D, Cotgrove A, Boddington E (2004) Selective serotonin reuptake inhibitors in childhood depression; systematic review of published versus unpublished data. *Lancet* 363:1341 - 1345
17. Zito JM, Derivan AT, Greenhill L (2004) Making Research Data Available: An Ethical Imperative Demonstrated by the SSRI Debacle. *Journal of the American Academy of Child and Adolescent Psychiatry* (in press) 43:509-511