Up for Debate

Pediatric Psychopharmacological Research in the Post EU Regulation 1901/2006 Era

Is There a Will and a Way? Experience and Perspectives of Lay and Expert Representatives in Germany

Christine Schmääl¹, Katja Becker², Ruth Berg¹, Michael Brünger³,
Gerd Lehmkuhl⁴, Klaus-Ulrich Oehler⁵, Thorsten Ruppert⁶,
Claus Staudter^{1,7}, Götz-Erik Trott⁸, and Ralf W. Dittmann¹

¹Research Group for Pediatric Psychopharmacology, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, ²Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Faculty of Human Medicine, Philipps-University of Marburg, ³Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Pfalz Institute, Klingenmünster, ⁴Department of Child and Adolescent Psychiatry, University Hospital Cologne, ⁵Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Practice, Würzburg, ⁶German Association of Research-Based Pharmaceutical Companies (vfa), Berlin, ⁷Ludwigshafen Association for Attention Deficit Hyperactivity Disorder, Ludwigshafen, ⁸Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Practice, Aschaffenburg, all Germany

Abstract. Although the use of psychotropic medications in child and adolescent psychiatry in Germany is on the increase, most compounds are in fact prescribed “off-label” because of a lack of regulatory approval in these age groups. In 2007, the European Parliament introduced Regulation 1901/2006 concerning medicinal products in pediatric populations, with a subsequent amendment in the form of Regulation 1902/2006. The main aim of this legislation was to encourage research and clinical trials in children and adolescents, and thus promote the availability of medications with marketing authorization for these age groups. Furthermore, initiatives such as the European 7th Framework Program of the European Union now offer substantial funding for pediatric pharmacological research. At a recent Congress of the German Society for Child and Adolescent Psychiatry and Psychotherapy (DGKJP), experts from the field and the pharmaceutical industry held a symposium with lay representatives in order to discuss attitudes toward, and experience with, pediatric psychopharmacology research in Germany since 2007. Several areas of concern were identified. The present paper derives from that symposium and provides an overview of these opinions, which remain crucial to the field. A wider discussion of how to facilitate psychopharmacological research in Germany in order to optimize the treatment and welfare of children and adolescents with psychiatric disorders is now warranted.

Keywords: psychopharmacological research/clinical studies, vulnerable/pediatric populations, pediatric investigation plan, marketing authorization.

Klinische Forschung in der Psychopharmakologie des Kindes- und Jugendalters, im Anschluss an die EU Regularie 1901/2006 – Intention und Möglichkeiten? Erfahrungen und Ansichten von Experten und Laien in Deutschland

Zusammenfassung. Obwohl ein Anstieg in der Verordnung von psychotropen Medikamenten in der Kinder- und Jugendpsychiatrie in Deutschland zu verzeichnen ist, wird die Mehrzahl dieser Substanzen weiterhin «off-label» verschrieben, da kaum behördliche Zulassungen für diese Altersgruppe vorliegen. Anfang 2007 wurde vom Europäischen Parlament die Regularie 1901/2006 zur Medikamentenentwicklung im Kindes- und Jugendalter eingeführt, ergänzt durch die Regularie 1902/2006. Das Hauptziel dieser Bestimmungen liegt darin, Forschung und klinische Studien mit Kindern und Jugendlichen anzuregen und damit die Verfügbarkeit behördlich zugelassener Medikamente für diese Altersgruppen zu unterstützen. Darüber hinaus ermöglichen Initiativen wie das Rahmenprogramm der Europäischen Union (FP7) erhebliche finanzielle Förderungen für klinische Studienaktivitäten im Kindes- und Jugendalter. Bei einem Kongress der Deutschen Gesellschaft für Kinder- und Jugendpsychiatrie (DGKJP) wurde von Experten aus diesem Fachgebiet sowie aus der Pharmazeutischen Industrie, unter Beteiligung von Vertretern von Angehörigen-Gruppen, ein Symposium abgehalten, um deren Einstellungen und Erfahrungen (seit 2007) zu und mit der Klinischen Psychopharmakologie Forschung in Deutschland zu diskutieren. Mehrere Bereiche wurden identifiziert, welche Schwierigkeiten bereiten bzw. Anlass zu Besorgnis bieten.

Schlüsselwörter: Psychopharmakologische Forschung/Klinische Studien, pädiatrische Population, pädiatrischer Prüfplan, Arzneimittelzulassung

Introduction

In Germany, the off-label prescribing of psychotropic medications for children and adolescents is widespread, despite the fact that this practice raises serious safety and ethical concerns (Kölch, Allroggen, & Fegert, 2009; Zito et al., 2008). Phasing-out off-label prescribing requires the availability of compounds that have received marketing authorization for these age groups, which in turn requires the existence of appropriate and well-regulated pediatric psychopharmacological research. In 2006, the European parliament introduced legislation on this issue (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm), thus indicating that these concerns have been recognized at the government level (Lehmann, 2008). Concerted efforts to facilitate pediatric psychopharmacological research are therefore warranted. The first step to this end lies in the identification of (1) practical obstacles to research and (2) the various ethical and other concerns of those involved.

This paper describes the opinions surrounding these two issues voiced by a group of lay and expert representatives from Germany. Wider and open discussion among both lay and expert groups in Germany is now called for in order to reach a consensus on future directions in the field.

EU Regulation 1901/2006

EU Regulation 1901/2006 concerning medicinal products in pediatric populations came into force in January 2007, with a subsequent amendment in the form of Regulation 1902/2006 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm). The legislation was introduced in response to concerns over suboptimal pediatric medication development in Europe and the resultant widespread practice of off-label prescribing (Lehmann, 2008). The regulation was modeled on existing legislation in the United States (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm0>

49867.htm). The overall aim of EU Regulation 1901/2006 is to ensure that children and adolescents are included in the mainstream medication development process in Europe (Lehmann, 2008). The major reasons for slow progress in the field prior to 2007 were twofold. First, as discussed by Tan and Kölch (2008), this research targets a doubly-vulnerable population from an ethical viewpoint, as these individuals are both (1) legal minors and (2) psychiatrically ill. Ironically, the reluctance to involve this population in research led to a situation where few pediatric clinical trials of psychotropic medication were being performed in Europe, making only scant data concerning short and long-term efficacy, tolerability, and safety available.

Table 1
Aims of EU Regulation 1901/2006

The specific aims of Regulation 1901/2006 are to:

- facilitate the development and accessibility of medical products for use in paediatric populations
- ensure that medicinal products used to treat paediatric populations are subject to ethical research of high quality
- ensure that these products are appropriately authorised for use in paediatric populations
- improve available information on the use of medicinal products in paediatric populations

Second, while the development of dosages and formulations for pediatric populations requires extra work and high costs on the part of the pharmaceutical industry, the revenue obtained from this relatively small population is limited and disproportionate to the investment required, which deters the pharmaceutical industry from more vigorous involvement. To address these issues, EU Regulation 1901/2006 now provides a legal framework for ethical pharmacological research in children and adolescents as well as incentives to the pharmaceutical industry (Lehmann, 2008). The specific aims of Regulation 1901/2006 are shown in Table 1.

Pediatric Investigation Plan

A key aspect of Regulation 1901/2006 is the introduction of the Pediatric Investigation Plan (PIP; www.ema.europa.eu/htms/human/pediatrics/pips.htm). The PIP was introduced to ensure that all new medications are evaluated at a very early stage for their potential value in pediatric populations, and that medicines for children are developed in tandem with medications for adults, albeit without delaying marketing authorization for adult or elderly populations.

Since 2007, pharmaceutical companies have been obliged to prepare a PIP for each new medication in Europe – even if the medication in question has no apparent value in these age groups – as well as for established medications that are to be developed for a novel indication. The PIP must explain precisely how the company plans to test the medication for its potential value in improving child health and well-being.

The PIP is scrutinized by a specific committee of the European Medicine Agency (EMA) established in response to EU Regulation 1901/2006, i.e., the Pediatric Committee (PDCO; http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000265.jsp).

After assessing the PIP, the PDCO grants one of the following: (1) approval (i.e., clinical trials in children or adolescents can commence following approval by the ethics committee and competent authorities); (2) a waiver (i.e., the PDCO agrees that clinical trials for this new medication are not necessary in children or adolescents); or (3) a deferral (i.e., the PDCO agrees that trials in children and adolescents will be necessary, but that it is not safe to conduct them at the present time, e.g., more data from adults are first required). This process also ensures that children are protected from unnecessary clinical trials.

The decision of the PDCO is legally binding. Adherence to the PIP is assessed by the PDCO during its “compliance check,” which is performed once the clinical trials have been completed.

Adherence to the PIP is of major importance during subsequent applications for marketing authorization.

EudraCT Database

To ensure transparency in ongoing and planned pediatric research in Europe following the introduction of Regulation 1901/2006, the EMA established the publicly accessible EudraCT website (<https://eudract.ema.europa.eu>). All pediatric clinical trials in Europe must be registered on this website. An important aim of this approach is to avoid unnecessary replication of pediatric clinical trials.

Status of Pediatric Clinical Trials Since the Introduction of EU Regulation 1901/2006

In July 2012, the PDCO published a 5-year report to the European Commission (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&mid=WC0b01ac0580025b8b), which states that since 2007 around 350 pediatric clinical trials per year were registered on the EudraCT website. Between 2007 and the end of 2011, PIP evaluation was completed for 682 medicines. Authorization was granted for 13 new medicines, 30 new indications, and 9 new pharmaceutical forms for pediatric use across all medical disciplines.

Only 2% of all agreed PIPs concerned child and adolescent psychiatry. Rewards to the pharmaceutical industry were granted for 12 medicines (Supplementary Protection Certificate (SPC) patent extensions for 11; Pediatric Use Marketing Authorization (PUMA) exclusivity for one). The PDCO concludes that pediatric drug development is increasing, and that the introduction of EU Regulation 1901/2006 has had a positive impact. However, on page 41 of its report (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&mid=WC0b01ac0580025b8b), the PDCO comments that it has been disappointed by the large number of healthcare professionals who do not recognize the need for evidence-based pediatric prescribing, and that this issue must be addressed.

Perspectives and Experiences of Pediatric Psychopharmacological Research Among Expert and Lay Representatives in Germany Since 2007

To evaluate the impact of EU Regulation 1901/2006 on child and adolescent psychiatry in Germany, lay and expert representatives exchanged perspectives and experiences at a recent Congress of the German Society for Child and Adolescent Psychiatry (DGKJP). The views expressed by each of these representatives have now been carefully updated and are summarized below.

Perspective of the Research-Based Pharmaceutical Industry (vfa) in Germany (Thorsten Ruppert)

Experience of German research-based pharmaceutical companies with the PIP process and the PDCO Members

of the German Association of Research-Based Pharmaceutical Companies (Verband der forschenden Pharma-Unternehmen in Deutschland, vfa; <http://www.vfa.de/>) shows that experience with the PIP procedure has been generally positive to date, even though discussions to establish an agreed PIP can be lengthy. However, certain aspects of the PIP procedure have proven difficult to implement.

First, the vfa has found that the PDCO very closely adheres to the agreed text of the PIP and expects an almost 1:1 implementation. As a result, even small deviations from the agreed plan prove problematic during the compliance check.

Second, vfa members noted that the PDCO occasionally imposes conditions that are difficult or even impossible to fulfill. These relate in particular to dosage forms, the requirement for studies in other age groups, and adherence to fixed time schedules.

Experience of vfa Members with the German Competent Authority (BfArM)

The vfa members report that experience with the responsible German authority (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM) since the introduction of EU regulation 1901/2006 has been generally positive with regard to the authorization of clinical trials involving children/adolescents. The vfa members found that BfArM takes a very pragmatic and constructive approach toward facilitating the commencement of clinical trials and bases its decisions on a sound scientific basis, which is thus fully comprehensible to the applicants.

Crucially, BfArM consults the PIP very closely when formulating its opinion and checks very carefully whether the recommendations of the PDCO have been followed.

One difficulty encountered in discussions with BfArM, however, concerns differences in expert opinion between EU and non-EU countries. For example, the sponsor of a multicenter clinical trial may have based medication dosages on prescribing recommendations from a non-EU state. However, BfArM tends to insist on adherence to the EU-prescribing guidelines at German study sites. This issue has arisen very recently in relation to an international pediatric psychopharmacology study involving German study sites (May 2013, addition by senior author).

Experience of vfa Members with German Ethical Review Boards

The situation concerning the approval of the German Ethical Review Boards (ERBs) is more complex, since several ERBs may be involved in the scrutiny of any given pediatric clinical trial. In Germany, a total of 53 ERBs assess pharmaceutical clinical trials, and experience with the ERBs is generally reported to be positive (Russ, Busta, Rie-

del, Zöllner, & Jost, 2009). However, no uniform standards for the granting of ethical approval are in place.

Thus, the respective German ERBs may have differing opinions on the same study with regards to issues such as study design, the qualifications of the investigators, and the suitability of the center.

As a result, certain centers may be viewed less favorably by a sponsoring pharmaceutical company during the selection of clinical sites for a given pediatric clinical trial. Furthermore, vfa members found that some study sponsors receive a large number of queries from ERBs, which may be inconsistent with, or redundant to, discussions with the PDCO.

A second area of difficulty for vfa members relates to documents/procedures concerning assent (from patients) and consent (from parents/legal guardians).

This issue is understandably of major importance to ERBs, and they insist that consent is provided by each individual legal custodian. In the case of parents or legal guardians who live together and/or share legal custody, both adults must sign a consent form before the child/adolescent can be included in a clinical trial.

A further assent-related stipulation is that the study investigator exclude any child who will be unable to recognize the nature, meaning, or consequences of the clinical trial once they reach the age at which they are able to give their explicit consent.

In Germany, an individual is considered an adult after their 18th birthday and would then be able to give consent. However, such a prediction is often very difficult to make for the study investigator, even in the case of a child who is currently psychologically healthy.

If this stipulation is overinterpreted, this could lead to difficulties in the conduct of the study, as study investigators may hesitate to include suitable patients. In the experience of vfa members, this has led to cases in which the study investigator has – quite rightly but based solely on personal uncertainty – decided to exclude otherwise suitable children from clinical trials in cases of doubt. Although these cases appear to be rare, this example demonstrates that a high degree of liability is placed upon the shoulders of the study investigators.

Another crucial point for study sponsors from the pharmaceutical industry concerns the definition of “minimal risk” within the context of a pediatric clinical trial. The PDCO bases its judgment of risk on International Conference on Harmonization (ICH) Guideline E11 (The European Agency for the Evaluation of Medicinal Products – Evaluation of Medicines for Human Use, Note for Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population, CPMP/ICH/2711/99, 2000), which specifies that risk and burden must be “minimized.”

However, German ERBs refer to the German Medicinal Products Act (Arzneimittelgesetz) (§41 (2) Satz 1 Nr. 2d; AMG (German Medicinal Products Act – German: Gesetz über den Verkehr mit Arzneimitteln (or: Arzneimittelgesetz – AMG); available from <http://www.gesetze-im-inter->

net.de/englisch_amg/index.html). This specifies that the clinical trial must involve “the lowest achievable minimal risk or burden.”

This may result in differences in interpretation of the study protocol between Germany and other countries, with potential implications for multicenter European studies.

Finally, the issue of “early termination criteria” for single study participants may raise problems in the case of disorders for which no objective, fixed termination criteria exist. In the United States and most European countries, ERBs accept that the decision to terminate the participation of a given patient is left to the discretion of the study investigator.

In Germany, however, some ERBs do not accept this approach. Instead they require that such “early termination criteria” be explicitly stated in the study protocol, and advise the study investigator to adhere to them. Overall, this shows that, although the conduct of pediatric clinical trials may result in some difficulties, the involved parties generally agree on a common scientific position.

It will be interesting to see whether the upcoming EU-regulation on clinical trials on medicinal products for human use (European Commission – Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 – available from http://ec.europa.eu/health/medicaldevices/files/revision_docs/proposal_2012_542_en.pdf) will ease the authorization of pediatric clinical trials throughout the EU.

Perspective of a German University Child and Adolescent Psychiatry Department (Gerd Lehmkuhl)

University hospitals have the duty to provide state-of-the-art treatment and to facilitate research; clinicians at these facilities therefore recognize and support the need for evidence-based treatment.

Furthermore, medical faculties favor participation in pediatric psychopharmacological studies, as this represents an important source of third-party funding. The involvement of university departments as study centers for such research is therefore encouraged. Nevertheless, a number of problems combine to render the participation of university departments in clinical trials problematic.

First, to conduct a clinical trial, the center must have an adequate infrastructure for the safe performance of study visits. The amount of funding allocated to a given center by a pharmaceutical company or a public sponsor is generally based on the number of cases recruited and the number of study visits to be performed. However, because of the difficulties experienced by many centers in the prompt recruitment of a sizable number of patients, this funding is often insufficient to support the facilities and staff required.

Second, even a university hospital may lack suitably qualified personnel. Pediatric psychiatric study nurses are scarce, and many clinicians lack the stringent qualifications required to function as a study investigator, as stipulated in the GCP-V (<http://www.gesetze-im-internet.de/gcp-v/>).

Third, recruitment of a sufficient number of patients at a university hospital study center may prove problematic in itself. University hospitals are often involved in multiple, parallel studies involving the same patient population, and these studies must compete with each in their recruitment.

Furthermore, the inclusion and exclusion criteria of pediatric clinical trials – which are necessary in order to meet requirements for regulatory approval/marketing authorization – are often so stringent that many patients fail the screening step (see Bliznak, Berg, Häge, & Dittmann, 2013). The principal investigator at a given site may also find it difficult to garner the interest of other senior colleagues in the recruitment process if they perceive no direct benefit to their patients and receive no form of reward for the extra work involved. Irrespective of how motivated the research team may be, convincing patients and their families that study participation is worthwhile often proves challenging.

Fourth, ERBs scrutinize pediatric psychopharmacological studies very closely, and the requirements of the German Medicinal Products Act (Gesetz über den Verkehr mit Arzneimitteln, Arzneimittelgesetz – AMG; available from: http://www.gesetze-im-internet.de/englisch_amg/index.html) have become much more stringent in recent years, leading to limitations on research involving legal minors and patients who are unable to provide assent.

In addition, ERBs may consider pragmatic clinical research designs (e.g., the addition of neuropsychology testing to the routine management of attention deficit hyperactivity disorder patients with medication) as being beyond “routine clinical care.”

As a result, the ERBs do not consider such studies to be “observational or noninterventional trials” (“Anwendungsbeobachtungen”), and categorize them instead as “clinical trials” (see EU Regulation 2001/20/EC; and the German Medicinal Products Act, §4, 23, 3; http://www.gesetze-im-internet.de/englisch_amg/). These then require more comprehensive study designs, including features such as more intensive monitoring, more complex ERB applications, provision of study medication, and a substantial increase in funding.

Perspective of a German Clinical Care Child and Adolescent Psychiatry Department (Michael Brünger)

The mission of clinical care hospitals is to provide effective healthcare, and these centers are under no contractual obligation to conduct research. Nonetheless, these hospitals represent a rich source of patients and are thus attractive

partners for research efforts. However, a number of issues render their active participation in pediatric psychopharmacological clinical trials problematic.

A major difficulty is the lack of appropriate resources. ERBs demand an appropriate infrastructure for the performance of pediatric clinical trials, which may be impossible to finance by a hospital with an already severely limited budget. Furthermore, appropriately trained personnel are lacking, in particular study nurses.

A further problem lies in the implementation of the stringent study protocols, in particular those based on a double-blind study design. Such an approach is often unfeasible for such a hospital facility, where patient care is managed by nonresearch teams and by nursing staff with no research experience, and this approach will not be accepted in severely ill patients.

Finally, the lack of time and motivation among staff are major hindrances to effective research participation. Research activities must be performed outside normal working hours by personnel who are already overburdened by routine clinical duties and on-call commitments. Participation in a large multicenter clinical trial does not (for various reasons) necessarily lead to study authorship, and the staff receives no financial or other reward for their research-related activities due to the absence of established reward mechanisms, such as extra contracts for financial reimbursement. For these reasons, clinical trial participation is unattractive to the majority of clinicians in nonacademic departments.

To overcome these difficulties, attempts have been made in individual hospitals to set up contractual agreements with the respective administrations in order to provide formal and adequate reimbursement for the extra hours worked by hospital staff (subinvestigators, study nurses) from the research budget allocated for a particular clinical trial.

Perspective of Two Office-Based Child and Adolescent Psychiatrists (Klaus Oehler, Götz-Erik Trott)

In Germany, over 90% of all psychotropic medications in children and adolescents are prescribed in office-based practice.

The issue of off-label prescribing and the implications of EU Regulation 1901/2006 are therefore of direct and practical concern to this professional group, and these clinicians have extensive experience of prescribing psychotropic compounds to these age groups. Nevertheless, the long-term personal experience of the present authors shows that over 90% of all pediatric psychopharmacological clinical trials are performed within a hospital setting.

There are three main reasons for the lack of involvement of office-based child and adolescent psychiatrists in pediatric psychopharmacological research.

First, most pediatric clinical trials are so underfunded that they can only be conducted in centers that employ clinicians in public service, thus excluding office-based practices. Second, recruitment often proves difficult because of the stringent inclusion and exclusion criteria applied in many pediatric clinical trials (see Bliznak et al., 2013). For example, a trial investigating treatment for depression may exclude patients with frequent suicidal thoughts or comorbid substance misuse.

Furthermore, many parents express concern at the possibility that their child will receive a placebo. Third, the study design is often too complex and impracticable for use in office-based practice.

Many child and adolescent psychiatrists in office-based practice are also skeptical of the value of the findings of pediatric clinical trials in/for their routine clinical work.

Although randomized placebo-controlled trials and meta-analyses have long been considered the gold standard for high-quality clinical research and as the evidence base for guideline development, skepticism as to their generalizability to a naturalistic practice setting is increasing (Bliznak et al., 2013; Parker, Anderson, & Haddad, 2003). The conditions imposed during these trials, such as narrow inclusion and exclusion criteria and complex study protocols, mean that everyday reality and routine clinical care are not reflected.

Thus, the results of such trials can be applied only to those narrowly selected groups investigated, and the effect of medication under genuine clinical conditions is not investigated. Meta-analyses in turn reflect only the content of these studies and so carry forward the weakness that they do not reflect clinical reality. As a result, many office-based child and adolescent psychiatrists often find the published results of such trials counterintuitive and opt to avoid research participation altogether.

Perspective of a Parent-Association for Attention Deficit/Hyperactivity Disorder (Claus Staudter)

Parents seek professional psychiatric help in order to allow both their child and their family life to return – as far as possible – to normality. They therefore attend the child and adolescent psychiatrist's office with the expectation of receiving practical and effective management.

With this in mind, patients and parents may feel somewhat let down when asked to participate in a clinical trial. Such a request may create the impression that their child is being asked to act as a "human guinea-pig," and that instead of focusing on the child's needs, the doctor is prioritizing his own scientific interests – or even those of the pharmaceutical industry.

Understandably, parents may want their child to receive an established form of therapy, rather than commit their

child and their family to a time-consuming research process with an unknown outcome or even to the possibility of complications or potential risks. This desire to avoid unnecessary risk could even be viewed by some members of society as the primary duty of parents or legal guardians.

A research process must offer some subjective sense of benefit to patients and their families if they are to assent/consent to participation, i.e., some aspect of the study must improve either the practical aspects of daily life or a child's functioning at school.

For this reason, studies involving some form of behavioral therapy tend to be more popular. In contrast, parents and patients tend to be wary of psychopharmacological studies, particularly those involving the possibility of placebo or a medication for which little information and data are available at the commencement of the study.

Even for families who are willing to accept the need for psychopharmacological research, the extra effort involved in study participation may represent an intolerable burden.

The stress involved in regular attendance at the study center, undergoing investigations not required during routine clinical practice, such as electrocardiograms and blood sampling, and the repeated completion of extensive questionnaires and interviews should not be underestimated. In particular for parents with other children or work commitments, time-consuming travel across the city, for example, to attend a weekly 2-hour appointment for 12 weeks (which is not unusual for registration trials) may simply be unfeasible.

Discussion

The above-mentioned symposium and subsequent experience and discussions have highlighted the fact that EU Regulation 1901/2006 has rendered the goal of ensuring safe and evidence-based prescribing among children and adolescents with psychiatric disorders attainable. Nonetheless, several areas of difficulty and concern were expressed, and these issues require further examination if appropriate research is to be facilitated, since suboptimal research efforts may increase both the number of studies required and the number of patients involved/placed at risk, and must therefore be considered unethical.

One major difficulty for both hospital-based and office-based psychiatrists is funding. Hospitals clearly require adequate funding for infrastructure and staffing, and office-based psychiatrists require appropriate reimbursement for the time and effort invested in research activities. In return for improved funding, the research process would gain extensive expertise and potential access to a wider range of population-based and hospitalized patients, and thus a speedier conclusion to clinical trials. It is therefore in the interest of both the pharmaceutical industry and public funding bodies such as the European

Commission to encourage their participation through increased funding.

In Germany, funding bodies such as the Deutsche Forschungsgemeinschaft (German Society for Research) and Bundesministerium für Bildung und Forschung (German Ministry of Education and Research), which are entirely independent of the pharmaceutical industry, should perhaps contribute more substantially to the performance of psychopharmacological studies in children and adolescents, in particular those related to clinically relevant topics and outcomes that reach beyond regulatory body requirements for registration.

Hospital-based psychiatrists and the pharmaceutical industry have also noted certain difficulties associated with the PDCO and ethical review processes, and efforts to relieve these problems would facilitate clinical trials.

In its 5-year report (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&mid=WC0b01ac0580025b8b), the PDCO expressed its openness to feedback and change, and the need to develop its processes on the basis of experience.

Liaison between bodies such as the EMA, the European Network of Research Ethics Committees (EUREC; <http://www.eurecnet.org/materials/index.html>), and the European Society of Child and Adolescent Psychiatry (<http://www.escap-net.org/>) might represent a starting point for positive change in this area.

The reservations of office-based child and adolescent psychiatrists toward clinical trials is another hindrance to research efforts, which raises the question of how more positive attitudes toward such research can be encouraged. The PDCO pointed out its disappointment at the large number of healthcare professionals who fail to acknowledge the need for evidence-based prescribing, and the profession must consider whether the need for an end to off-label prescribing is genuinely recognized and accepted.

Wider availability of established pediatric psychopharmacology training seminars is recommended to overcome reservations on the part of clinicians.

Research clearly shows that the rate of pediatric psychotropic prescribing is on the rise (Dalsgaard, Nielsen, & Simonsen, 2013; Wong, Murray, Camilleri-Novak, & Stephens, 2004; Zito et al., 2008), a fact that highlights the need for an increase in the number of registration trials. In addition, to address the needs and questions of clinicians from routine clinical settings, registration studies should be followed up and complemented by naturalistic, observational trials ("Anwendungsbeobachtungen"), which allow assessment of the use of the respective medication for a given indication and/or population in that environment.

Patients and their family are, of course, central to any research effort, and their concerns must be addressed if progress is to be made. Greater awareness of the biological nature of mental illness, the rationale for psychopharmacological treatment, and recognition that inadequate treatment may have long-term adverse consequences for the patient may increase understanding of why clinical trials are indicated. A

wider availability of adequate and tailored information for the lay public, parents, and patients concerning the rationale and practical implementation of clinical trials is recommended.

Media Liaison

The medical profession should perhaps be more proactive in approaching the media in order to present information about mental illness in these age groups, rather than merely responding to “bad press.” Close liaison with the relevant self-help organizations is also essential if the profession is ever to eradicate the view that children and adolescents are being recruited as “human guinea-pigs.” Nevertheless, patients and their families clearly require some form of practical assistance during the research process, e.g., more comprehensive and frequent visits and assessments, in order to offer more intensive care and support for the patient and their family than can be provided in current routine settings.

Beyond that, possible options would include consultation concerning issues beyond the objectives of the study as well as the reimbursement of travel costs and the provision of insurance to cover study visits.

In summary, the introduction of EU Regulation 1901/2006 represents legal recognition of the fact that the stepwise phasing-out of pediatric off-label prescribing should commence as soon as this becomes feasible. This can, however, be achieved only by acquiring appropriate data within clinical trials and by obtaining regulatory approval – and thus marketing authorization – for all medications used in these age groups.

However, success can be assured only through a positive commitment to the research process by professionals, families, the media, and all groups with an interest in the welfare of children and adolescents. An important task for all concerned is to achieve a consensus for ameliorating the difficulties involved in performing such research. Both the present paper and the symposium upon which it was originally based serve to stimulate this important process.

Conclusion

EU Regulation 1901/2006 established a framework for responsible pediatric psychopharmacological research (as initiated by the pharmaceutical industry or by others such as university-based sponsors). Improved public funding for such research is now available.

To reduce the off-label use of psychotropic compounds in child and adolescent psychiatry – and that is the intent of EU Regulation 1901/2006 – all those involved must acknowledge (1) the need for robust clinical data and (2) the fact that these data can only be obtained through well-designed clinical trials leading to the granting (or refusal) of regulatory approval and marketing authorization.

An expert symposium and subsequent discussions revealed various residual areas of difficulty in the conduct of

such research, and the contributors offered diverse suggestions as to how this situation could be improved. These ideas now require further discussion and expansion.

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Date initially submitted: 20 December 2013
Date revision accepted: 31 March 2014
Conflicts of interest: None

Disclosures

Katja Becker was involved in research/clinical trials with Eli Lilly and Shire and is on the Advisory Board of Eli Lilly/Germany. She was paid for public speaking by Eli Lilly and Shire and received conference attendance support from Shire and Eli Lilly. She also receives or has received research funding from the German Research Foundation (DFG), the German Federal Ministry of Health (BMG), the German Federal Ministries of Research and Education (BMBF) as well as local research funding from the University Hospital of Giessen and Marburg (UKGM).

Ralf W. Dittmann is a former employee of Eli Lilly & Company and owner of Eli Lilly stock. He has served in advisory and consultancy capacities for Janssen-Cilag, E. Lilly, Otsuka, Shire, and Theravance. He has received conference attendance support and speaker's fees from E. Lilly and Shire. He is or has been involved in clinical trials conducted by Ferring, Janssen-Cilag, Eli Lilly, Otsuka, and Shire. He has also received research funding from the US National Institute of Mental Health (NIMH), the European Union (FP7 Programme), the German Research Foundation (DFG), the German Federal Ministries of Research and Education (BMBF) and Health (BMG/BfArM), and the Volkswagen Foundation. The present work is unrelated to the above-mentioned relationships and grants.

Gerd Lehmkuhl is a member of the Eli Lilly advisory Board on Atomoxetine.

Klaus-Ulrich Oehler presented lectures on behalf of Shire, Eli Lilly, Novartis, Medice, and Janssen-Cilag. He is an advisory board member for Shire, Eli Lilly, and Medice. He received remuneration for participation in clinical trials from Shire, Eli Lilly, Novartis, Medice, Janssen-Cilag, Otsuka, Pfizer, GSK, Boehringer-Ingelheim, Sanofi Aventis, Lundbeck, and Schwabe.

Thorsten Ruppert is an employee of the German Association of Research-Based Pharmaceutical Companies (Verband Forschender Arzneimittelhersteller e. V. – vfa).

Götz-Erik Trott received honoraria for talks from AstraZeneca, Janssen-Cilag, Medice, Novartis, Pfizer, and Ratiopharm. He has also been a consultant, a member of an advisory board, and/or a speaker for Janssen-Cilag BV, AstraZeneca, Medice, Novartis, Pfizer, Bristol-Myers Squibb, Shire, and Lilly.

The other authors have no conflicts of interest to declare.

Ralf W. Dittmann MSc, MD, PhD

Research Group for Pediatric Psychopharmacology
Department of Child and Adolescent Psychiatry and
Psychotherapy
Central Institute of Mental Health
Medical Faculty Mannheim, University of Heidelberg
J5
D-68159 Mannheim
Germany
Phone +49 621-1703-4924
Fax +49 621-1703-4545
ralf.dittmann@zi-mannheim.de