A Comparison of Life Stages and Cultures in the Use of Antipsychotic Medications for the Treatment of Anxiety Disorders

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Many of the researchers in the uses of antipsychotic medications have shown concern over the paucity of specific studies of the effectiveness and side-effects of antipsychotic drugs on specific populations, especially vulnerable patients like children and pregnant women, and people of non-American cultures. This paper is intended to give some perspective on what we know and do not know concerning the use of such medications on these populations. An additional concern is the reliability of leaving diagnosis, prescription and administration in the hands of general practitioners rather than specialists. In addition, we observe a trend for patients themselves to over-medicate, often under commercial pressure from the pharmaceutical industry.

Many of the studies cited herein show concern for sensitive populations like young children, adolescents, the elderly, those with comorbidity factors, pregnant and nursing women, and cultural differences. This current paper endeavors to illuminate research gaps, which will allow the psychological and psychiatric groups to serve such people better. The methodologies under discussion in the various papers did not show any remarkable distinctions with respect to region, country, or ethnicity; matters of side-effects, comorbidity factors, length of effectiveness, patient compliance, drug interactions, dangers of tolerance and addiction, and need for reliable standards and guidelines, were consistent among the regional studies. This paper intends to show the need for clearer, more updated and comprehensive policies and standards, more funding for larger studies so that drug interactions and the needs of marginalized groups can be understood and treated more effectively and safely.

Literature Review

Issues concerning treatment by general practitioners were examined in several research articles found in my library search (Boonstra, Grobbee, Hak, Kahn, & Burger, 2011; Bandelow, 2008). Numerous papers compared the effectivity of SSRIs to other anti-anxiety treatments (Bakker, van Balkom, & Spinhoven, 2002; Mogg, Baldwin, Brodrick, & Bradley, 2004; Crupi, Marino, & Cuzzocrea, 2011; McIntyre & Katzman, 2003; Moncrieff, Cohen, & Mason, 2009; Stahl, 2004; Vasile, Bruce, Goisman, Pagano, & Keller, 2005).

Various studies investigated the merits of official guidelines in treating anxiety disorders (Bereza, Machado, Ravindran, & Einarson, 2012; Manthey *et al*., 2011). Some articles addressed issues concerning the administration of antipsychotic medications to children (Cummings & Fristad, 2007; Graham *et al*., 2011; Pao & Bosk, 2011). Some research focused on geriatric treatment of mood disorders (Kastenschmidt, & Kennedy, 2011). Elderly people, similarly to children, have different metabolisms from those of adults in the normally-studied age ranges. Social anxiety disorder (SAD) was the focus of a paper by Hindmarch (2009).

Concerning anxiety treatments in countries and regions outside of the U.S.A., I found several articles for Canada (Bereza, Machado, Ravindran, & Einarson, 2012; Katzman, 2009; Yatham *et al*., 2009), for the Netherlands (Boonstra, Grobbee, Hak, Kahn, & Burger, 2011; Manthey *et al*., 2011), and for Spain (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008; Kauer-Sant'Anna, Kapczinski, & Vieta, 2009), one for Taiwan (Chen, Chen, & Wang, 2012), and another done in Turkey (Kartal, Coskun, & Dilbaz, 2010). One paper (Graham *et al*., 2011) studied the present issues for Europe as a region. In addition, a paper by the former editor-in-

chief of the New England Journal of Medicine (Angell, 2000) on how profit motives are driving drug prices out of reach.

Methodology

The main procedure of this paper was to examine the current literature on the use of antipsychotic medications on understudied populations, and also the off-label uses made of the drugs on those populations. To be determined was how much of a gap there is in the reported research with the intent of focusing more efforts on these populations. I compared the methodologies and results of the various papers under consideration, and formulated conclusions therefrom concerning the general state of research on the subject populations.

I first searched the PsyInfo database for 'anxiety' and "antipsychotic or SSRI or SGA or typical" in "All Text." I then searched the Medline database for those same elements in the 'Title' field and derived the results cited in this proposal. In addition, I made use of references to these subjects in the popular media and searched for their scholarly sources.

Discussion

General Notes on Uses and Observations of Antipsychotic Medications with Anxiety Disorders

We will begin with a brief survey of the effectiveness and toleration of several antipsychotic medications. In general, tricyclic antidepressants (TCAs) proved equally effective to serotonin reuptake inhibitors (SSRIs) for panic disorder, but with dropouts for the latter comprising only 58% of the former, in one study (Bakker, van Balkom, & Spinhoven, 2002).

Another study affirmed the effectiveness of SSRIs as well as of serotonin norepinephrine reuptake inhibitors (SNRIs), TCAs, and pregabalin, with similar toleration issues for TCAs as mentioned above (Bandelow, 2008). For treatment-resistant cases, the author cautiously recommends benzodiazepines, monoamine oxidase inhibitors (MAOIs), and quetiapine along with other atypicals. Issues to consider were given as expense, tolerance, and likelihood of addiction.

Crupi, Marino, and Cuzzocrea (2011) proposed that anxiety and related mood disorders were strongly related to neuroplasty and neurotransmitter receptors. They offered several drug and non-drug treatments, including antiglucocorticoid therapies and transcranial magnetic stimulation (TMS), but the ones of particular interest in this current paper are the second-generation antipsychotics (SGAs). Of these, the authors singled out aripiprazole, as an adjunct to SSRIs for treating anxiety, in addition to its effectiveness for mood disorders in general.

Aripiprazole was also the subject of an experiment to determine its effectiveness for, among other symptoms, anxiety due to withdrawal from long-term dopaminergic treatments by sufferers of Parkinson's disease. The key issue was to determine what treatments would alleviate such symptoms without increasing extrapyramidal side-effects. The advantage with aripiprazole turned out to be its partial agonism at D_2 receptors, although that advantage is lessened in cases of psychosis comorbid with Parkinson's (Mizushima, Takahata, Kawashima, & Kato, 2012).

Many researchers are interested in the extent to which cognitive bias of ambiguous information exacerbates the symptoms of generalized anxiety disorder (GAD). One study (Mogg, Baldwin, Brodrick, & Bradley, 2004) found that a short duration four to six weeks) of

SSRI treatment for such patients lowered both the degree of the cognitive bias and also the level of anxiety. After initial assessments, 19 GAD patients were given either paroxetine or citalopram for four weeks, and then reassessed for interpretive bias, anxiety, and depression, all showing significant reductions.

A paper by Moncrieff, Cohen, and Mason (2009) examined 439 comments posted on an Internet site in order to generalize experiences and issues with antipsychotic medications from subjective insights of users. Of these postings, 223 concerned risperidone, 170 were about olanzapine, and another 46 comments referred to three first-generation antipsychotics (FGAs). The respondents complained of grogginess, sexual problems, suicidal thoughts related to akathisia, extrapyramidal features with the older medications, and emotional flattening, but there were some positive responses in terms of mood stabilization: 31% for risperidone, 34% for olanzapine, and 26% for the FGAs.

Stahl (2004) explained how the selective binding properties of SSRIs can be matched against each other to produce combinatorial therapies for complex syndromes, such as anxiety and apathy with insomnia. This paper showed that even what may ordinarily be considered to be side-effects can be utilized to advantage with a proper understanding of secondary binding properties.

Despite the effectivity and safety advantages of SSRIs, benzodiazepines (BZDs) remained the preferred treatment in a 12-year longitudinal study in the New England Harvard/Brown Anxiety Disorder Research Program (Vasile, Bruce, Goisman, Pagano, & Keller, 2005). Instead of, as one might expect, attempting to predict recovery rates for patients who were taking BZDs and SSRIs, this study reversed the research question and asked, instead, how

many were still taking the medications after the duration of the study. The number of subjects seemed sufficient, beginning with 179 generalized-anxiety-disorder (GAD) patients and 176 social-phobia patients, but conclusions were hampered by 1) having to rely on patients' reporting of their own medications and treatments, 2) having an insufficiently diverse population, 3) being limited to a relatively small geographical boundary (New England), 4) insufficient adherence to the 1998 treatment guidelines, and 5) uncorrelated comorbidities among the subjects. These factors contributed to a lack of firm conclusions.

Research in Canada

One Canadian study reviewed 50 research articles on GAD in order to validate the clinical guidelines of the Canadian Psychiatric Association (CPA). The authors utilized the Hamilton Anxiety Rating Scale (HARS) to assess response, remission, and mean-reductions, and Review Manager-5 to pool results on a random-effects model (Bereza, Machado, Ravindran, & Einarson, 2012). They concluded that, although there were predictable improvements in response and reduction from first-line over second-line drug classes, no clear trends could be authenticated from their study; they expect that their data will benefit future research on guideline effectiveness.

Katzman (2009) asserted that, because GAD is so prevalent and of high cost to the individual and to society, the primary treatment should be either an SSRI (e.g., escitalopram, paroxetine, sertraline) or an SNRI like duloxetine or venlafaxine, despite some side-effects, a two- to four-week delay in relief, and a drop-off in efficacy. Therefore, atypical antipsychotic medications (SGAs) showed promise as alternatives.

Another Canadian study (Yatham *et al*., 2009) reviewed the effectiveness of drug and non-drug therapies for anxiety as a common comorbidity with bipolar disorder (BPD). The authors found that anxiety comorbidity was a significant predictor of poor recovery from BPD (especially among elderly patients), along with ADHD, alcohol use, use of antidepressants, treatment non-compliance, low socio-economic level, and being female. Using the Hamilton Anxiety Scale (HAS) and the Clinical Global Impressions (CGI-Severity) scale, the study found that adding either olanzapine or lamotrigine to the standard lithium therapy produced significant improvements over a 12-week period; risperidone, on the other hand, did not show similar benefits.

Research in the Netherlands

A Dutch review of the prescribing practices of general practitioners (Boonstra, Grobbee, Hak, Kahn, & Burger, 2011) found, as the authors expected, that off-label use of antipsychotic medications, for treating anxiety and depression, favored typical rather than atypical medications. The difficulty with the Dutch registration system is that anxiety is always taken as part of the "anxiety and depression" combination. This fact is unfortunate for papers such as this present one, because anxiety is treated differently from depression regarding drugs and therapies.

Another study from the Netherlands (Manthey *et al*., 2011) examined the extent to which BZDs were used according to official guidelines. The researchers found that the elderly and chronically ill patients were at particular risk of overuse or usage past recommended durations, although single groups, the unemployed, and those taking other medications also overused BZDs (82% of the ~428 BZD users in the Netherlands Study of Depression and Anxiety – NESDA – database).

Research in Spain

For a perspective on the effect of drugs on Spanish women, an experiment was conducted on six women who suffered from chronic post-traumatic stress disorder (PTSD) due to sexual attacks (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008). This research, conducted with a combination of psychotherapy and low doses of 3,4-Methylenedioxymethamphetamine (MDMA or *ecstasy*), was originally designed to include 29 women, but was forced to finish prematurely due to political pressures. Although the research could not be completed, safety at the stated doses was established and effectiveness seemed quite promising, so it was expected that the design and data from this study would provide a foundation for a large-enough study to be able to draw clinically usable conclusions.

Another Spanish study (Kauer-Sant'Anna, M., Kapczinski, F., Vieta, E. (2009) focused on anxiety disorders as comorbid with bipolar disorder (BPD). The authors demonstrated positive results with quetiapine, fluoxetine, olanzapine, and lithium, but risperidone gave unsatisfactory outcomes. Of greatest concern was that, since treatment for BPD is already complex by the nature of the disease, it would be exacerbated by comorbid anxiety and that, therefore, the practitioner should use extra diligence in those cases.

Research in Taiwan

Some experiments using atypical antipsychotic medications failed to show a significant benefit. For example, a study in Taiwan (Chen, Y. C., Chen, C. K., & Wang, L. J. (2012) tried extended-release quetiapine (Q-XR) on 26 volunteers (plus another 13 on placebo) who suffered from either primary or comorbid anxiety over an eight-week period. The subjects were appropriately screened and were evaluated, in part, with the 14-item Hamilton Anxiety Scale

(HAM-A). Despite the rigor of the experiment, no significant improvement was found with the administration of the Q-XR.

Research in Turkey

A Turkish research project (Kartal, Coskun, & Dilbaz, 2010) studied the effectiveness of treatment of anxiety disorders by primary healthcare providers. These treatments generally included a combination of psychotherapy and psychopharmacology, conducted by 255 physicians with various levels of training in psychopharmacology; those with post-doctoral education in psychiatry gave more accurate diagnoses, as expected. The rates of correctly prescribing SSRIs for diagnoses were 59% for SAD, 33% for generalized anxiety disorder (GAD), and 55% for OCD.

Research on Children

With respect to children with mood disorders, Cummings and Fristad (2007) indicated that therapists were not so much concerned with anxiety in the youngsters as they were with hyperactivity, psychosis, or BPD. The SGAs they discussed were Risperidone and olanzapine, either alone or as adjuncts to other therapies. However, the authors pointed out that, often, the risk-to-benefit ratio would lean toward fewer drugs administered to children, due to the paucity of studies to determine the risks of side-effects and other safety issues.

Meanwhile, a European study (Graham et al., 2011) found that drugs targeted for ADHD did not pose any significant safety risk for children with anxiety disorders, although the use of stimulants tended to reduce growth rates (weight more than height), especially for children between three and five years of age. The significance of that study for this current paper is that

anxiety is frequently associated with ADHD. The drugs tested included methylphenidate, dexamfetamine, atomoxetine, and methylphenidate.

A study sponsored by the National Institutes of Health and the National Institutes of Mental Health (Pao & Bosk, 2011) examined the high rate of anxiety in medically ill children. The primary recommendation for treatment was cognitive behavioral therapy (CBT), but when this did not prove sufficient, the authors studied the effectiveness of several medications of which, specifically for anxiety symptoms, SSRIs were considered safe and effective for both children and teens. The other medications they considered were for depression and OCD.

Social Anxiety Disorder (SAD)

SAD was studied in a paper on cognitive impairments due to treatment with psychopharmacological agents (Hindmarch, 2009). Those which caused least cognitive impairment were SSRIs; fluvoxamine caused little impairment, whereas sertraline was responsible for five times the SSRI average of impairment. As expected, benzodiazepines caused significant cognitive impairment. This research was done by analyzing research articles, on the subject, which were published between 1975 and 2007.

Anxiety Comorbid with Bipolar Depression (BPD)

BPD is complex to diagnose and treat in the first place, but with the comorbidity of anxiety, it can be quite challenging (McIntyre & Katzman, 2003). Such a combination of syndromes can cause greater severity of symptoms, misdiagnosis, greater frequency of episodes, and lesser response to drug treatments. Without having conclusive data for effectiveness, the authors observed positive benefits, on subjects with BPD, OCD, and bipolar mania, with such atypical antipsychotics as risperidone, olanzapine, and fluoxetine.

A Critique of the Pharmaceutical Industry

Angell (2000) discussed the fact that drug costs were increasing at approximately 15% per year, and were soon to exceed physicians' services and all other healthcare costs. Even with drug benefits added by government (under discussion as of time of publication, but implemented since then), profits have replaced the pharmaceutical industry's original mission of serving humanity by finding and producing cures for our ailments. According to the author, these costs have made many important medicines out of reach for (anxiety) disorder populations considered too small to budget studies for, and those in third-world countries. Therefore, many people needlessly suffer due to high costs of extant remedies which could save their lives and restore them to health and productivity. The report contended that the cost burden is easily within reach of the large pharmaceutical companies, which dominate the drug market, but that they are reluctant to accept that responsibility, demanding favorable concessions in governmental policy.

Conclusions

It is becoming clear to the research community that a "one size fits all" research policy does not serve sensitive populations like young children, adolescents, the elderly, those with comorbidity factors, pregnant and nursing women, and cultural differences. The observations in this current paper endeavor to illuminate research gaps; doing so will allow the psychological and psychiatric communities to serve such populations better. The methodologies under discussion in the various papers did not show any remarkable distinctions with respect to region, country, or ethnicity; issues of side-effects, comorbidities, duration of effectiveness, patient compliance, drug interactions, risks of tolerance and addiction, and need for trustworthy standards and guidelines, remained consistent across all political boundaries. The greatest distinctions were found for the vulnerable populations mentioned above and for cultures (e.g.,

Asian, African) which favor naturalistic remedies over pharmaceuticals. Finally, the question was raised as to whether we are over-medicating the population with ever-more-expensive drugs. This trend appears to be induced by the profit motive of the pharmaceutical industry, and possibly by a passivity of practitioners in accepting the concomitant sales pressure.

Future Research Needed

Many of the cited papers called for clearer, more updated, and more comprehensive policies and standards. Calls for funding of larger studies, in order to draw more reliable conclusions, were prevalent, especially for marginalized or vulnerable populations. Left to the profit-incentives of drug companies, such classes of sufferers would not have conclusive enough research accomplished, so government funding was recommended. In particular, more research was shown to be needed to understand drug-drug interactions, especially in cases of comorbidity. Finally, it is hoped that national governments will continue to become more supportive of alternative medications, such as the treatment of PTSD with MDMA. There has been progress, more in Switzerland than in the U.S., but more freedom and budgeting is needed for such promising treatments.

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