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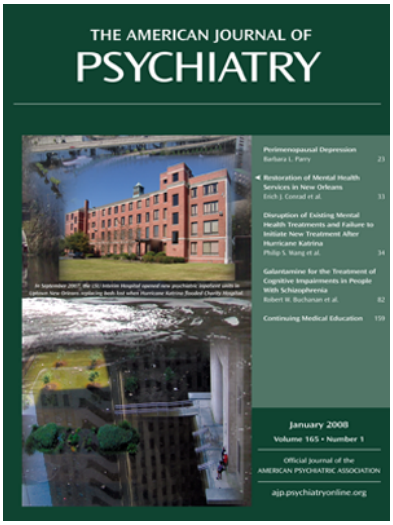

The following is an interview with Patricia Suppes, M.D., Ph.D., on "The Pharmaceutical Industry and Its Influence on Academic Psychiatry," conducted by Aashish Parikh, M.D. Dr. Suppes is a Professor of Psychiatry and Director of the Bipolar Disorder Research Program at the University of Texas Southwestern Medical Center. Dr. Suppes also serves on the Editorial Board of the American Journal of Psychiatry. *Dr. Parikh, the Resident Editor for this issue, is a fourth year resident in child and adolescent psychiatry with Austin Medical Education Programs.*

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1) How interdependent are academic psychiatry and the pharmaceutical industry?

Their overall agendas are different, with work in academia directed toward scientific advancement and patient care in a general nonprofit setting, while the pharmaceutical industry generally operates in a "for profit" mode, directing advancement and informing decisions. The "for profit" is often seen as negative. However, it also motivates innovation and collaboration with scientists on the newest developments.

2) Are there any methods that are commonly used to make a particular medication appear more useful than the raw data indicates?

I think this happened more in the past than it does now. The required reporting of clinical results on federal web sites (e.g., www.clinicaltrials.gov), as well as strong reviews on this issue has generally moved industry to fully report both positive and negative results. In general, when academic partners are involved in writing up results, a fairly common practice, pharmaceutical representatives are respectful and supportive of academic input and suggestions. Most of the pivotal trials include an academic partner, and so in many cases it actually falls to the academic partner to responsibly confirm the absence of bias and full reporting. In some sense, this partnership provides useful checks and balances.

3) What advice can you provide on evaluating potential bias in grand rounds presentations, Continuing Medical Education (CME) activities, and journal supplements?

I think it is important to note the industry sponsor(s) and assess the material for full reporting, rather than focus on a given product. One hopes that current changes in the pharmaceutical industry, coupled with increased regulations, will make this less of an issue in the future.

4) What is a "ghostwritten" article and how common is this practice in psychiatry?

This varies quite a bit. "Ghost writing" generally means that the first draft or portions of the first draft are put together by a secondary media company (or division of a pharmaceutical company focusing on scientific publication). This is fairly common, but does not necessarily mean there is not substantial input and editing by the individual employed at the academic institution. Again, I do not think this is an intrinsically "bad" practice, if the academic partner does its due diligence and is actively involved in the final article. This implies that the academic partner truly makes the article its own, versus a product from the company.

5) Have there been any positive changes in psychiatry since the implementation of the Pharmaceutical Research and Manufacturers of America (PhRMA) code on interactions with health care professionals in 2002?

Yes. For example, I think the industry is more cautious and thoughtful about input into CME activities. Some companies have always behaved in an ethical manner, in that they did not get involved in CME, but overall the field is better now that these limits are more clearly spelled out and regulated.

6) Recently, a few major academic medical centers have implemented polices that ban direct interaction with the pharmaceutical industry. How might these policies affect patient care?

Many of these policies seem quite positive, with more clear regulations on interactions between academia and industry. It is likely that this trend will continue. One concern I have about this trend is the removal of patient medication samples at major academic institutions. This is an understandable limitation, but it makes it more difficult for patients, in that the initial dose needed is not always known at the outset of treatment, nor if a specific medication will be well tolerated. This could make it more difficult and costly for patients to initiate needed medication.

7) What are some of the common pitfalls residents encounter when researching a newly approved medication?

One pitfall is obtaining information on a new medication from only one source. Another pitfall might be basing opinion and practice on clinical views without reviewing the evidence.

8) Is it useful for residents to read pharmaceutical advertisements or be "detailed" by pharmaceutical representatives, or "reps"?

This is a difficult question. I would answer both yes and no. Reps can provide useful information about "their" medication. But it is up to residents to read the science and consider how other medications compare.

9) What resources would you recommend to residents when researching a medication?

In my area of bipolar disorder, I generally read primary research. For other areas, the monthly newsletter *Biological Therapies in Psychiatry*, produced by Dr. Alan Gelenberg, is helpful, and APA's *Psychiatric News* and other similar publications often have good summaries.

10) What is your opinion on the following three examples of interactions between residents and the pharmaceutical industry?

1. Departmental policy does not allow residents to use branded pens, notepads, or staplers, yet the department accepts thousands of dollars worth of textbooks each year.

My guess is this is a practice that will soon fade out. I am not familiar with this type of policy, but I also would find this confusing.

2. Attendance is mandatory at case conferences, where lunch is provided by a pharmaceutical company (worth $200 to $300), yet reps are not allowed to mention their product.

Again, this is a practice that is unlikely to continue. This is an intermediate effort to regulate interaction with pharmaceutical reps, with mixed results.

3. During rounds, a resident recommends a generic medication for a patient and a strongly "pro-pharma" attending physician recommends a more expensive enantiomer, prodrug, or metabolite of the generic version.

I'm not sure what "pro-" or "anti-pharma" truly means, as our first concern is hopefully always the patient. If a more expensive drug is being recommended, there should be data on safety, tolerability, or efficacy to support this practice. When conducting the Texas Medication Algorithm Project (TMAP), my colleagues and I always recommended starting with the most well tolerated form of a medication to increase the likelihood of adherence. Some drugs have tolerance data, and some do not. Thus regardless of the physician's involvement with the industry, the question should always be, "What is the evidence?"

11) What direction is future industry-academia interaction headed?

I expect there will be increased regulation over the next few years. Not so much to block interaction but to prevent future abuses, such as a few individuals have engaged in. I see regulation as a good trend overall, and hopefully it will increase transparency in academic and pharmaceutical interactions. Many ongoing psychiatric research efforts require funding from a variety of sources to maintain an effective operation. As NIH and NIMH funding is expected to be flat for the next few years, pharmaceutical funding for investigator-initiated and multisite studies is likely to continue to be an important source of funding for researchers in academic institutions. The collaboration between academic and pharmaceutical enterprises is an important one in the long run for advancing patient care.

Velocardiofacial Syndrome-Associated Psychiatric Illness and Response to Aripiprazole: A Case Study

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Velocardiofacial syndrome, or 22q11.2 deletion syndrome, is the most common known microdeletion syndrome, occurring in approximately 1 of 4,000 live births (1). This syndrome is often undiagnosed, in part because of a lack of awareness by clinicians, but also because many cases present with variable and mild phenotypic expression. Four central congenital features of the syndrome include 1) cleft palate or velopharyngeal insufficiency, 2) cardiac malformations, including ventriculoseptal defects and tetralogy of Fallot, 3) dysmorphic facial features, including narrow palpebral fissures, long philtrum, thin upper lip, large nose with large tip and a prominent nasal root, and small cupped ears, and 4) borderline to mild mental retardation and language disorders. Additional findings include immunodeficiency and hypocalcemia (1).

Childhood psychiatric manifestations of velocardiofacial syndrome include attention deficit hyperactivity disorder (ADHD), anxiety disorders, mood dysregulation, and autism spectrum disorders (2). Adults with the syndrome show minimal resolution of psychiatric symptoms (3). In approximately 32% of individuals with velocardiofacial syndrome, chronic psychosis presents between late adolescence and early adulthood, and most of these cases meet the criteria for schizophrenia (3).

Velocardiofacial syndrome is the most common known genetic risk factor for schizophrenia (3). Several genes located in the base pair deletion involving 22q11.2 are presently implicated in the pathogenesis of psychosis. However, the most studied gene in the 22q11.2 region is catechol *O*-methyltransferase (COMT), an enzyme responsible for the breakdown of dopamine. As such, the syndrome serves as a research model for studying the neurobiological basis for the evolution of multiple psychiatric disorders across the lifespan. More studies of psychopharmacological treatments for psychiatric illnesses associated with velocardiofacial syndrome are needed. We describe the case of an adult male with velocardiofacial syndrome and lifelong psychiatric problems who presented with recent onset of delusions, which were treated successfully with the antipsychotic aripiprazole.

"Mr. A" was a 24-year-old white male subject with features of velocardiofacial syndrome, including a long face, prominent nasal root and tip, small cupped ears, a ventriculoseptal defect at birth, cleft palate, juvenile rheumatoid arthritis, recurrent otitis media, and frequent skin infections. Velocardiofacial syndrome and the 22q11.2 deletion were confirmed by fluorescence in situ hybridization at the age of 23 years. The patient's history included rages, ADHD during childhood, anxiety, and a rigid preference for sameness regarding toys and food items, diagnosed as pervasive developmental disorder not otherwise specified. At the age of 13 his full-scale IQ was 81, which decreased to 67 by age 23. From the age of 19 he demonstrated increasing irritability, impulsivity, and verbal outbursts. Between the ages of 19 and 22 he had taken money from two separate employers and served jail time, despite returning the money. He subsequently experienced paranoid delusions that the police were pursuing him and his parents were plotting to harm him. At age 22 he assaulted his father, stating that his father's throat clearing indicated that his father planned to hurt him. During outpatient treatment, he was unresponsive to several medication trials, including sertraline, escitalopram, venlafaxine, quetiapine, donepezil, and metyrosine, a competitive inhibitor in the biosynthesis of dopamine.

The patient was hospitalized at age 23 for depression, suicidal ideation, rage, irritability, and persecutory delusions. He was diagnosed with bipolar disorder with psychotic features. Treatment with 15 mg/day of aripiprazole resulted in sustained improvement with regard to outbursts of anger, mood stability, and compulsiveness and anxiety. There have been no recurrences of delusions to date.

A search of the literature for antipsychotic treatments for velocardiofacial syndrome produced only one other case report, in which 150 mg of clozapine was administered twice daily, producing marked improvement in an adult with velocardiofacial syndrome-associated psychosis (4). Risk factors for developing chronic psychosis for the syndrome include marked childhood anxiety or depression, low verbal IQ, and possessing the COMT low-activity allele (3).

Velocardiofacial syndrome is the most common known genetic risk factor for developing chronic psychosis, and its diagnosis is increasing. Patients with this syndrome represent a candidate study group for a large controlled trial to identify treatments of chronic psychotic illness associated with this genetic disorder.

As clinicians, it is important to identify individuals with velocardiofacial syndrome and confirm its clinical diagnosis with genetic testing, and to collaborate with basic science researchers to advance our knowledge of this syndrome.

Dr. Hellings is a consultant with Abbott Laboratories. Drs. Brewington and Butler report no competing interests. The authors thank Drs. Monica F. Kurylo and Albert Poje for their initial referral and neuropsychological testing of this patient.

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Schizophrenia With and Without Comorbid Depression

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Comorbid depression is common among patients diagnosed with schizophrenia and is associated with substantial morbidity, including increased risk of suicide (1). Comparison studies of differences between patients meeting criteria for schizophrenia with comorbid major depressive disorder and patients meeting criteria for schizophrenia without comorbid major depressive disorder are rare. Differences between these two groups in sociodemographic, family, clinical, and treatment histories are important, as they may affect clinical management practices and ultimately treatment outcomes (2–5). The purpose of this study was to define the differences between these two patient groups.

Method

Subjects were all new patients (1,458) between 1981 and 1986 in a large psychiatric outpatient clinic. Patients were assessed during their initial visit using a structured diagnostic interview, a complete psychological history, and the Symptom Checklist 90-R (SCL-90-R). Of these patients, 192 (13%) met the diagnostic criteria for schizophrenia, and 136 (71%) satisfied diagnostic criteria for major depressive disorder in addition to schizophrenia. No protocol for treatment was provided and as such, all patients involved received standard clinical treatments.

Results

Sociodemographic differences between the two subject groups were not statistically significant. First-degree relatives of subjects with schizophrenia with comorbid major depressive disorder had significantly higher rates of alcohol-related problems and somatization disorder, compared with first-degree relatives of subjects without major depressive disorder (50% versus 18%; $p<0.0004$, and 30% versus 14%; $p<0.05$, respectively). Rates of depression or schizophrenia among first-degree relatives were not significantly different between the two subject groups. Similarly, compared with subjects without comorbid depression, subjects with comorbid depression had significantly greater rates of obsessive-compulsive disorder (39% versus 14%, $p<0.0008$), phobias (22% versus 11%, $p<0.05$), panic attacks (35% versus 7%, $p<0.0001$), and manic episodes (52% versus 9%, $p<0.0001$).

In both male and female subjects, the SCL-90-R symptom profiles of subjects with comorbid depression showed significantly higher levels of current distress than the SCL-90-R symptom profiles of subjects without comorbid depression. Clinical history also revealed fewer childhood psychiatric diagnoses in the subject group without comorbid depression, along with better physical health, less stress, less difficulty getting along with others, fewer problems managing financial affairs, and greater self-satisfaction.

There were no statistically significant differences between the two subject groups in use of psychiatric services; however, there were differences in type of pharmacologic treatment received. Antidepressants were used more often among subjects with comorbid depression compared with subjects without comorbid depression (45% versus 12%, $p<0.0002$). Subjects with comorbid depression also reported more subjective improvement in depressive symptoms with the use of antidepressant medications. Neuroleptics were used more often among subjects without comorbid depression (85% versus 57%, $p<0.001$).

Discussion

Differences between subjects with schizophrenia with comorbid depression and subjects without comorbid depression included higher familial rates of alcohol-related problems and somatization disorder, as well as higher rates of comorbid obsessive-compulsive disorder, phobias, panic attacks, and mania. Prior studies have shown poor outcomes in subjects with schizophrenia and comorbid depression, and that comorbid depression contributes to these outcomes.

There is little evidence available in the literature to guide clinicians toward effective treatment strategies among this subpopulation of patients. Controlled studies are warranted to identify the most effective treatments for schizophrenia with comorbid depression.

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