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Polypharmacy and Adverse Drug Reactions

To the Editor: I read with interest the article about antipsychotic polypharmacy by Kreyenbuhl and colleagues in the April issue (1). The authors concluded that the patients who were on long-term antipsychotic polypharmacy were more severely ill with psychotic symptoms. The inference was partly based on increased odds of hospitalization in the previous year among patients who received more than one antipsychotic drug.

Antipsychotic polypharmacy has been linked to a greater incidence of adverse reactions (2), which in turn may lead to increased hospitalizations (3). The average age of patients in the study was more than 50 years; thus the likelihood of hospitalizations as a result of medication side effects is even higher. Kreyenbuhl and colleagues also note that the patients who were receiving polypharmacy were taking more antianxiety medications, mood stabilizers, and anti-Parkinsonism drugs, which further increases the risk of adverse drug reac-

tions. An important determining factor in hospital admissions related to adverse drug reactions among elderly persons is the number of drugs being taken (4).

Kreyenbuhl and colleagues acknowledged the possibility of increased incidence of adverse reactions but did not consider it as a confounding factor in the study. It is conceivable that the hospitalizations among patients taking more than one antipsychotic were a reflection of the adverse drug reactions rather than the severity of illness.

Antipsychotic polypharmacy is a widely prevalent practice without any robust evidence to back it up. More studies are needed before this practice can be justified on empirical grounds.

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In Reply: We appreciate Dr. Babbar's letter, which brings much needed attention to a serious safety concern—hospitalization for adverse drug reactions, which could result from treatment with multiple antipsychotic medications. We share his concern about this and other potential adverse consequences of a treatment

strategy that lacks solid evidence for its efficacy and safety.

Dr. Babbar correctly notes that patients prescribed antipsychotic polypharmacy in our study were more likely to receive several other psychiatric medications, which could further increase their risks of adverse effects and subsequent hospitalizations. In addition, patients receiving polypharmacy were prescribed antipsychotic dosages that were the same as or higher than for those receiving monotherapy and had greater use of anti-Parkinson agents, which suggests that they were at risk of or were already experiencing side effects related to excess antipsychotic exposure. These findings lend further support to Dr. Babbar's hypothesis that rather than reflecting the severity of patients' psychotic symptoms (a potential indication for the use of polypharmacy), the higher rate of past-year psychiatric hospitalization was a result of the adverse effects of multiple medications.

The overall goal of our study was to describe patient characteristics and treatment patterns associated with long-term antipsychotic polypharmacy. Although the safety and effectiveness of antipsychotic polypharmacy are important and unresolved issues, evaluating the outcomes of this treatment strategy was beyond the scope of our cross-sectional investigation. Further, we were not able to determine the reasons for the hospitalizations in question, although we do know that they reflected admissions to psychiatric or addiction treatment units. It is also important to note that the psychiatric hospitalizations occurred in the year before the period during which we documented patients' antipsychotic and other psychotropic treatments. We have no information regarding the medications prescribed before these admissions. This led us to infer that the previous hospitalizations were indicators of the severity of psychiatric illness of patients receiving antipsychotic polypharmacy, a conclusion reached by others who have reported a similar association

between polypharmacy and previous hospitalization (1–3).

Patients with refractory and disabling psychiatric symptoms (that may be reflected in increased use of inpatient psychiatric services) may be more likely to receive complicated psychotropic regimens that in turn induce adverse effects severe enough to result in hospitalization. We agree with Dr. Babbar that more research is needed to determine the extent to which this may be happening in routine clinical practice.

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Pilot Test of Seeking Safety Treatment With Male Veterans

Seeking Safety (1) is a manualized treatment protocol designed to simultaneously treat substance use disorders and posttraumatic stress disorder (PTSD). This innovative approach was originally created for and has been empirically validated with female trauma survivors (2–4).

In designing and proposing the first randomized controlled treatment trial of Seeking Safety with men with substance use disorders and PTSD, we consistently heard concerns about the application of this “female-oriented” approach to men. There were concerns about an excessive focus on sexual trauma, presumably uncommon in men; lack of focus on combat trauma; and general gender bias in the wording—for in-

stance, examples of physical abuse are from the perspective of the victim rather than the perpetrator. Only after assurances that we would first pilot-test the program with a group of men and would make necessary changes to the manual were our protocols approved. It should be noted that because we were motivated by the prospect of writing a new version of—or supplement to—the manual, any bias on our part was in favor of revising the program.

In 2006 we conducted a 12-week pilot test of Seeking Safety with male veterans in methadone maintenance treatment at a Department of Veterans Affairs (VA) mental health clinic before the initiation of a five-year randomized controlled trial. We then conducted a semiformal focus group of volunteer participants to ask about general concerns, such as what we could improve, and specific concerns, such as whether the examples of sexual trauma were a problem. We also asked a male researcher and a male veteran who was also a counselor to review the protocol for gender-biased language. In addition, we consulted extensively with the therapist who ran the pilot therapy sessions and the therapist’s clinical supervisor, the latter of whom has extensive experience training and supervising clinicians to conduct Seeking Safety.

Without exception, the consensus was that the protocol did not need substantive gender-related changes to work well with our population of male patients with substance use disorders and PTSD. For instance, despite specific concerns, sexual trauma examples helped our participants who had a relevant history discuss this more “taboo” form of trauma, perhaps for the first time. In contrast, those with primarily combat trauma very readily brought the general concepts to bear on their experience. In our view, this phenomenon actually increased the need for sexual trauma examples, while decreasing the need for additional explicit combat examples. No protocol modification could have kept combat trauma from being a prominent focus in our

groups. Modifying the focus away from sexual trauma could actually have exacerbated inequality in our group and reinforced avoidance of sexual trauma issues.

Careful wording in the Seeking Safety protocol also appears to avoid appreciable gender bias. For instance, the manual discusses domestic violence in terms of “violent” or “unsafe” relationships. Rather than reading a victim bias into this, even men who were perpetrators agreed that their relationships were “violent” or “unsafe.” Similar examples exist throughout the manual.

Although initial concerns that Seeking Safety would need significant adaptation for use with men made excellent clinical sense, the consensus of our experts and consumers indicates that this does not appear to be the case. The careful construction of the manual appears to allow for adaptation as a natural part of the group process. Although these observations are preliminary, they challenge the notion that Seeking Safety as currently written is inappropriate for use with male veterans.

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Suicide in Japan

To the Editor: Many previous studies have found mental disorders to be the most powerful risk factor for suicide in all age groups, accounting for 80% to 90% of all completed suicides (1–3). To inform prevention efforts, it is important to determine the rate of psychiatric treatment among persons who commit suicide and to document demographic characteristics of those who do not receive treatment. However, to our knowledge no longitudinal study has examined these issues in a large sample over a long period.

We examined data on gender, age, and psychiatric treatment for all suicide victims over 21 years of age ($N=5,161$) from 1981 to 2001 in the city of Kobe, Japan (population of approximately 1.5 million in 2003). Data were compiled by the Medical Examiner's Office of Hyogo Prefecture and published in its annual reports. Statistical analysis was performed by using t tests and chi square tests. A probability level of .05 was regarded as statistically significant. The data were analyzed with SPSS software, release 10.07J. This study was approved by the ethical committee of Niigata University Graduate School of Medical and Dental Sciences.

Three-quarters of persons who completed suicide (73.7%) did not receive psychiatric treatment in the

year before the suicide. The rates of psychiatric treatment in the sample were almost constant over the study period. Psychiatric treatment was more common among females than males (39.9% and 19.3%, $\chi^2=252.0$, $df=1$, $p<.001$). Elderly persons who completed suicide, especially those in their seventies and eighties, were significantly less likely than younger persons to receive psychiatric treatment in the year before suicide ($\chi^2=195.3$, $df=1$, $p<.001$). Middle-aged persons—those in their forties and fifties—who did not receive psychiatric treatment in the year before suicide accounted for 30% of all completed suicides; more than 80% of this high-risk group was male.

The psychiatric treatment rate in this study was much lower than those in previous studies, which ranged from 45% to 60% (4). However, Asukai (4) found a treatment rate of 22.9% among Japanese persons who attempted but did not complete suicide, although the sample was very small. Thus Japanese persons who attempt suicide tend to be less likely to receive psychiatric care than those in Western countries. Recently, Kobe has become one of several large Japanese cities in which many psychiatric clinics are available. Despite this trend, three-quarters of those who committed suicide over the past two decades in Kobe did not receive psychiatric treatment. Although low rates of psychiatric treatment among persons who commit suicide can sometimes be attributed to a lack of psychiatric clinics, this is not the case in Japan. In addition, suicide does not void large payouts by life insurance companies in Japan (5), which may spur some persons to

commit suicide to maintain the economic welfare of their families. In Japan, therefore, it is very important to build a system of public health care and encourage persons with suicidal ideation to consult a psychiatrist. Efforts to improve suicide prevention strategies among middle-aged men are especially needed.

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