Core Concepts Involving Adverse Psychotropic Drug Effects

Assessment, Implications, and Management

Joseph F. Goldberg, MD[a,*], Carrie L. Ernst, MD[a,b]

KEYWORDS

• Nocebo • Adverse effects • Adverse event • Pharmacogenetics • Iatrogenic
• Drug safety • Drug tolerability

KEY POINTS

- Adverse drug effects occur in more than half of patients taking medications for major psychiatric disorders; but their potential to jeopardize treatment adherence often depends on patient expectations, adverse effect severity, illness severity, alternative pharmacotherapies, and viable ways to manage the adverse effects.
- Patient characteristics that may increase the risk for developing adverse effects include negative treatment expectations, suggestibility, emotionality, proneness to somatization, phobic-obsessive traits, slow metabolizer phenotypes, and historical sensitivity to adverse drug effects.
- Pharmacogenetic markers are beginning to yield useful information about patient-specific vulnerabilities to certain adverse drug effects and overall adverse effect severity.
- A systematic approach to the assessment of suspected adverse drug effects can help optimize therapeutic outcomes.

Adverse effects from psychotropic drugs account for nearly 90,000 annual visits to emergency departments in the United States,[1] yet their management remains among the least studied problems within clinical psychopharmacology. Sheer suspicion about the possible presence of a drug adverse effect brings together concerns

Disclosure: In the past 12 months, J.F. Goldberg has been a consultant to Myriad Genetics, Sunovion, WebMD, and Medscape. He has served on the speakers' bureau for AstraZeneca, Janssen, Merck, Sunovion, Vanda Pharmaceuticals, and Takeda-Lundbeck. He has received an editorial stipend from Frontline Medical Communications and royalties from American Psychiatric Publishing, Inc., United States. C.L. Ernst has received royalties from American Psychiatric Publishing, Inc., United States.

[a] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, Gustave L. Levy Place, Box 1230, New York, NY 10029, USA; [b] Department of Medical Education, Icahn School of Medicine at Mount Sinai, Gustave L. Levy Place, Box 1230, New York, NY 10029, USA
* Corresponding author. 128 East Avenue, Norwalk, CT 06851.
E-mail address: joseph.goldberg@mssm.edu

Psychiatr Clin N Am 39 (2016) 375–389
http://dx.doi.org/10.1016/j.psc.2016.04.001 **psych.theclinics.com**
0193-953X/16/$ – see front matter

regarding pharmacodynamics, pharmacokinetics, pharmacogenetics, psychosomatics, psychodynamics, treatment expectations, drug adherence, and the therapeutic alliance. Because drugs do not differentially exert beneficial versus adverse consequences, it falls to the prescriber to understand fully the end-organ effects of a given medication, alongside the plausibility, time course, dosing relationships, drug interactions, and interplay of pharmacodynamic and psychological factors that collectively become manifest as physical, behavioral, and cognitive-emotional symptoms.

This article reviews basic concepts related to the aforementioned considerations involving the assessment and management of putative adverse effects of psychotropic drugs. The authors first consider the extent to which patient and prescriber expectations about possible adverse effects can influence treatment outcome, alongside patient- and medication-specific factors that seem to moderate the emergence of adverse drug effects.

IMPACT OF ADVERSE EFFECTS ON ADHERENCE: ANTICIPATION VERSUS ACTUAL OCCURRENCE

Rates of nonadherence to psychotropic medications due specifically to adverse effects, or at least the perception of adverse effects, have been reported to range from 14% (in bipolar disorder[2]) to 30% (in schizophrenia[3]). Among depressed older adults who newly begin an antidepressant, adverse effects accounted for about a 5% increase in the probability of treatment discontinuation.[4] Presence of somatic symptoms of depression at baseline may especially predict discontinuation due to adverse effects during antidepressant treatment.[5]

Magnitude and severity of adverse effects also influence outcome; among depressed patients at a 3-month follow-up, incurring one or more rated as being "extremely bothersome" adverse effects increased the chances of antidepressant discontinuation by 150%, but adverse effect presence alone (or less severe adverse effects) did not.[6] Treatment discontinuation due to adverse effects also may correlate with higher doses of selective serotonin reuptake inhibitors (SSRIs).[7] *Initial* adverse effects from SSRIs during depression treatment do not seem to increase the likelihood of premature discontinuation in SSRI clinical trials for major depression.[8]

Although adverse effects are often presumed to contribute prominently to medication refusal or nonadherence, attitudes and expectations about medication effects may actually play a more fundamental role. For example, *fear* of possible adverse effects[9] and general beliefs that medications cause harm[10] are more common among drug-nonadherent than adherent patients who have mood disorders. Negative expectations about drug effects also correlate more strongly with *subjective* than *objective* manifestations of putative adverse effects.[11] In the Texas Medication Algorithm Project, patients' negative beliefs about possible harmfulness of medications significantly predicted discontinuation of treatment at both 6 and 12 months.[12] Another study of antidepressant prescribing in primary care found that fears and concerns about adverse drug effects, but not concerns about illness, significantly predicted nonadherence.[13] In schizophrenia, poor antipsychotic medication adherence has been linked with suspected drug-related adverse effects that are more psychological (eg, poor concentration, anxiety, and fatigue) than somatic.[14]

PREDICTORS OF ADVERSE DRUG EFFECTS

A dilemma arises when deciding how best to counsel patients about the likelihood of an adverse effect without generating greater expectations for their occurrence. On the