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Lisa Cosgrove and Emily E. Wheeler

Introduction

The profession of medicine is predicated upon an ethical mandate: first do no harm. However, critics charge that the medical profession's culture and its public health mission are being undermined by the pharmaceutical industry's wide-ranging influence. In this article, we analyze how drug firms influence psychiatric taxonomy and treatment guidelines such that these resources may serve commercial rather than public health interests. Moving beyond a conflict-of-interest model, we use the conceptual and normative framework of institutional corruption to examine how organized psychiatry's dependence on drug firms has distorted science. We suggest that academic-industry relationships have led to the corruption of the evidence base upon which accurate diagnosis and sound treatment depend. We describe the current dependency corruption and argue that transparency alone is not a solution—and sometimes even produces iatrogenic effects. Furthermore, we argue that the corruption of the evidence base for diagnostic

and practice guidelines renders obsolete the traditional informed consent process, and we offer suggestions for reforming this process.

Corruption of Diagnostic Guidelines

When the American Psychiatric Association (APA) published the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) in 1952, there were no antianxiety agents, antidepressants, or antipsychotics on the market, and psychiatry embraced a psychoanalytic model. Outside of psychoanalytic circles, *DSM* diagnoses (of which there were few) had little professional and no cultural currency. But the manual that few had ever heard of in 1952 is now frequently referred to as the "bible" of psychiatric disorders and the most current edition, *DSM*-5, is integral in sustaining the multibillion-dollar psychopharmacology market. Indeed, the *DSM*, through its increasing congruence with the *International Classification of Diseases*—the classification system used by most countries—affects health care globally.

Because the *DSM* standardizes symptom criteria and codifies psychiatric disorders, it plays a central role in health and disability claims, insurance coverage, and court cases such as custody disputes and cases involving defense on the grounds of mental illness. Although the use of the *DSM* among all clinicians addressing mental health concerns, not just psychiatrists, makes it an important source of revenue for the APA, accounting for 46 percent of its 2011 revenue from publications,[1] the *DSM* also has a profound monetary impact that extends well beyond sales, due to its effect on many diverse domains.

For example, the *DSM* plays an important role in the approval process for new drugs and in the regulatory process for extending patents of previously approved medications. The U.S. Food and Drug Administration (FDA) requires an identifiable psychiatric condition before it will

consider granting approval of an application for a new psychotropic medication, thereby creating an "economy of influence"[2] among authors of diagnostic and treatment guidelines, drug regulators, and drug manufacturers. In fact, some critics have referred to the relationship amongst the *DSM*, the FDA, and Big Pharma as an "unholy alliance." Thus, it is not surprising that, shortly after the task force for the *DSM*-5 was established in 2007, critics charged that corporate interests, particularly those of the pharmaceutical industry, might be influencing the *DSM* revision process.

Concerns about industry influence and, concomitantly, the exponential rise in prescriptions for psychotropic medications stem from the fact that, with each revision of the *DSM*, the APA has increased the number of diagnostic categories. The first *DSM* identified 106 disorders, but by the time the *DSM*-IV Text Revision was published in 2000, the number had almost tripled. Also, the *DSM*-III marked a paradigm shift in the conceptualization of psychiatric diagnosis, a shift that turned out to be fortuitous for drug firms. Robert Spitzer, who chaired the *DSM*-III, was committed to replacing the "pseudo-scientific" framework of earlier editions with an emphasis on empirical validity and reliability. He wanted to develop a psychiatric nosology that was reliable, valid, and disease-oriented rather than merely descriptive. The *DSM* adopted the biopsychosocial model, which explicitly links the biological and psychological. Spitzer also removed references to psychoanalytic theory, such as the term "neurosis," and instead included specific symptom and threshold criteria in an explicit attempt to increase diagnostic reliability.[3]

The emphasis on verifiable symptoms and the adoption of the disease model helped to secure psychiatry's reputation as a *medical* specialty at a time when its professional reputation was in question.[4] This elevation in status continues to give psychiatry—and thus the *DSM*—legitimacy, but it also opened the door to an improper dependence on industry. It is the

promotion and dissemination of the *DSM* as a scientifically valid and empirically based instrument that fosters acceptance of a disease model of mental disorders. This view is embraced by drug firms and believed by the general public. Although it was not the APA's or Spitzer's intention to develop a psychiatric manual that was an industry-friendly instrument, Spitzer later acknowledged that "[t]he pharmaceuticals were delighted"[5] with the model the *DSM*-III adopted.

However, it is not only the adoption of the disease model for classifying mental disorders that allowed psychiatry's dependency corruption to develop. Unlike *individual*—or quid pro quo—corruption, which occurs when "bad or bent souls"[6] engage in clearly unethical and illegal behavior (such as research fraud), dependency corruption results when an *organization* is no longer sufficiently independent to pursue its stated goals or mission effectively. That is, systematic practices develop within that institution that are legal, accepted, and normative, but that nonetheless undermine its integrity.[7] Unwittingly, organized psychiatry developed policies, financial incentives, and behavioral norms that created an improper dependence on industry—improper in the sense that the processes for generating knowledge about the etiology and treatment of mental illness became compromised. The APA, as an organization, compromised its scientific objectivity through a growing dependency on drug firms and by internal interests (such as guild interests) and external influences (such as third-party reimbursement practices incentivizing psychiatrists to act as psychopharmacologists rather than as talk therapists). Practices that allowed for a deviation from organized psychiatry's public health mission—and that also led to a distortion of scientific truths—became normalized.

For example, in 1980, the year the APA adopted the disease model of mental disorders, it also voted to allow pharmaceutical companies to sponsor scientific symposia at its annual conference. This not only markedly increased the flow of pharmaceutical money into the APA, it

also altered the content of the symposia. The APA's annual revenues rose from $10.5 million in 1980[8] to $65 million in 2008,[9] by which time at least $14 million came from pharmaceutical companies,[10] in the form of ads in the APA's journals (*American Journal of Psychiatry*, *Psychiatric Times*, and *Psychiatric Services*), sponsorship of scientific symposia at its annual conferences, advertising booths at those conferences, and various "educational" grants.

Another example of the distortion of truths that occurred because of psychiatry's dependency corruption can be seen in the way that the *DSM*-IV and *DSM*-5 extend the biopsychosocial disease model that began with the *DSM*-III. Despite the explicit linking of the biological and psychological in the *DSM*-5, *there are no biologic markers* (i.e., a substance, physiological characteristic, gene, etc., that indicates the presence of disease) *for any DSM disorder*. Allen Frances, who chaired the *DSM*-IV, sums this point up well:

> The incredible recent advances in neuroscience, molecular biology, and brain imaging that have taught us so much about normal brain functioning are still not relevant to the clinical practicalities of everyday psychiatric diagnosis. The clearest evidence supporting this disappointing fact is that not even *one* biological test is ready for inclusion in the criteria sets for *DSM*-5.[11]

It is this very disease model and its assumption that mental illness has a clear neurochemical etiology that makes the *DSM* vulnerable to industry capture. In fact, criticisms of "disease mongering" emerged as soon as the APA announced proposals for new disorders in the *DSM*-5. Disease mongering refers to (a) the sponsorship of disorders by pharmaceutical companies in order to create markets for new drugs and (b) the widening of diagnostic boundaries in an effort to expand an existing drug market. Ray Moynihan, Iona Heath, and David Henry[12] described efforts by drug manufacturers to encourage the public to think about diffuse symptoms as identifiable and valid diseases or disorders that can be treated with medications, thereby creating a risk of overdiagnosis—the diagnosis of a clinical entity in an individual

without having met the criteria for that entity—and overtreatment.[13] One example is Eli Lilly's rebranding and relicensing of its blockbuster drug Prozac (fluoxetine hydrochloride) as the drug Sarafem for the treatment of Premenstrual Dysphoric Disorder (PMDD). (The application for a new indication for Prozac/Sarafem occurred just as Lilly's patent on fluoxetine was about to expire.[14]) Before Sarafem's approval, a roundtable discussion article was published[15] that supported both the existence of PMDD as a "distinct clinical entity" and the effectiveness of antidepressants as a treatment for it; the roundtable included several doctors, FDA representatives, and members of Eli Lilly's staff. The majority of *DSM*-IV panel members for PMDD had financial ties to Eli Lilly.

Researchers and clinicians have questioned the validity of some of the new disorders in the *DSM*-5, such as Disruptive Mood Dysregulation Disorder[16] and Binge Eating Disorder.[17] Perhaps the most controversial revision was the elimination of the bereavement exclusion from the diagnostic criteria for a Major Depressive Episode. With this change, individuals who are actively grieving a loss are no longer distinguished diagnostically from individuals who experience depressive symptoms without such a loss. Some psychiatrists have argued that this revision is a step toward diagnostic accuracy, if bereaved depression and clinical depression are understood as similar symptomatically if not etiologically.[18] Others, including the former chair of the *DSM*-IV, Allen Frances,[19] have made the case that the revision would create a "false positive problem" resulting in the overdiagnosis of depression and big opportunities for industry profit.

In 2007, in an attempt to restore public trust and facilitate the practice of good science, the APA published a policy requiring individuals involved in the *DSM* revision process to disclose any relationships to industry within the three calendar years preceding their appointment, to be updated annually for the duration of their participation. (The current

standards can be read online.[20]) The APA believed that its disclosure policy was robust and would restore public trust. Yet, a comparison of *DSM*-IV and *DSM*-5 panel members showed that despite the increased transparency, commercial ties remained strong; 69 percent of the *DSM*-5 task force members reported financial ties to industry, a 21-percent increase over the *DSM*-IV task force. The persistence of these ties despite the APA's disclosure policy shows that transparency and attempts to "manage" financial conflicts of interest cannot prevent the appearance, if not the reality, of bias in clinical decision-making.

Also, three-fourths of the work groups continued to have a majority of members with ties to drug firms, and it is noteworthy that, as with the *DSM*-IV, the most conflicted panels for *DSM*-5 were those for which pharmacological treatment is the first-line intervention (that is, the recommended course of action). For example, 67 percent of the panel for mood disorders, 83 percent of the panel for psychotic disorders, and 100 percent of the panel for sleep/wake disorders (which now includes "Restless Leg Syndrome") have ties to the pharmaceutical companies that manufacture the medications used to treat these disorders or to companies that service the pharmaceutical industry.[21] The extent of conflicts of interest among these work groups reveals how important it is to examine the systemic and institutional practices that allow for these conflicts and that reinforce them as normative. Indeed, the implications of APA's dependence on industry and of the economies of influence that sustain this dependency need to be made explicit.

Clinical Practice Guidelines, the "Funding Effect," and Institutional Corruption

Over 20 years ago, the Institute of Medicine (IOM) disseminated recommendations on Clinical Practice Guidelines (CPGs).[22] The assumption at the time was that the guidelines would be

trustworthy because they would be an unbiased, empirically derived set of recommendations. They would be useful because they would contain a decision tree or algorithm to guide the busy clinician inundated with too much—and sometimes contradictory—information. Thus, CPGs are intended to enhance the practice of evidence-based medicine by streamlining health care delivery and improving the process and outcomes of patient care. Additionally, insurance companies rely heavily on guidelines when deciding which treatments they will pay for and, although there is no rule that CPGs must be used, they are seen as an integral part of evidence-based medicine.

As with diagnostic guidelines, clinical care guidelines in psychiatry are vulnerable to industry capture because the absence of biological markers for mental disorders increases clinical uncertainty. Increasingly, CPGs, especially those produced by industry-tied professional groups, have been criticized for being essentially marketing tools for drug companies[23] rather than being based on sound evidence. Bias in psychiatry CPGs creates the potential to expose many patients to harm from unnecessary treatment or from treatment that is not evidence-based. Because partnerships between commercial entities and academe are increasingly the norm, it is necessary to examine current practices and policies intended to protect against industry's capture of clinical guidelines. In the section below, we discuss why disclosure is not enough of a safeguard to prevent bias in psychiatric guidelines.

If evidence-based medicine is to have real meaning, it is imperative to critically evaluate research results published by individuals or medical specialty groups with commercial ties. There is a strong and well-documented connection between funding source and study outcome, known as the "funding effect."[24] Researchers who examine the relationship between funding source and study outcome have consistently shown that results are favorably biased toward the funder.[25] The problem is so pernicious that some researchers[26] have called for a moratorium on

guidelines produced by specialty groups and the Institute of Medicine's most recent recommendations for guideline development recommended that guideline developers free themselves from, rather than simply disclose, financial conflicts of interest.[27]

Clearly, implementing the IOM's recommendations are an important step in preventing bias.[28] However, the focus on conflicts of interest may deflect attention from the real problem—institutional practices. Carl Elliott sums this point up well:

> The difficulty with conflict of interest as a way of framing the problem of industry funding is that it directs our attention to individuals…. [T]his way of framing the issues makes it sound as if these financial ties are a purely individual problem—that an individual has a problem and we need to manage it.[29]

Hence, the problem is not quid pro quo corruption involving the individual "bad apple"; the problem is the "bad barrel."[30] The conceptual and normative framework of institutional corruption sheds light on the fact that the funding effect is not the result of research fraud but rather is sustained by practices that are legal and often well-accepted within the professional group or organization. Cases of individual researchers engaging in research fraud or pharmaceutical companies engaging in illegal activities make headlines, yet it is a mistake to focus on individuals or to believe that corporate greed is the problem.[31] The root of the problem is organized psychiatry's improper dependence on industry, the economies of influence and guild interests that sustain this dependence, and the alliances that are formed as a result (such as those involving the FDA, APA/*DSM* panel members, and drug companies).

For example, pharmaceutical companies' mission statements give the impression that they are fully dedicated to serving the public good. Nevertheless, corporate officers have a responsibility to serve their shareholders' interests and market pressures demand that they increase their shareholder value. Thus, the primary aims of drug firms are not always congruent

with public health and medical goals; organized psychiatry's dependence on those firms inevitably corrupts the development of diagnostic and clinical guidelines. Addressing this dependency corruption is particularly difficult because well-intentioned researchers truly believe that their financial relationships with pharmaceutical companies do not influence their decision-making and interpretation of data. As Darrel Regier, co-chair of the *DSM*-5 told *USA Today* in response to critics who noted that 90 percent of the authors of three major psychiatry CPGs had ties to drug firms: "There's this assumption that a tie with a company is evidence for bias. But these people [APA's CPG authors] can be objective."[32] Contrary to Regier's optimistic belief, it is unrealistic to expect authors of clinical guidelines to achieve what the rest of us cannot: to remain consistently and completely unbiased in the face of a competing interest (see the article by Sunita Sah and Adriane Fugh-Berman in this issue).

But Regier's view is not surprising; studies have shown that physicians strongly believe that commercial ties do not bias their clinical choices despite substantial research demonstrating that they typically do.[33] There is a wealth of data illustrating how difficult it is for individuals to remain neutral or be objective when they have a personal stake in a particular outcome.[34] And that is why financial transparency will never eliminate bias. Partnerships with commercial entities such as drug firms foster "pro-industry habits of thought, that are difficult, if not impossible, to monitor and manage."[35] A powerful example of this kind of pro-industry habit of thought can be seen in a recent study of meta-analyses of hypertensive drugs. There was poor concordance between results and conclusions in such meta-analyses when the researchers had financial ties to drug firms, but there was good concordance when the researchers had financial ties to nonprofit groups.[36] The discordance between results and conclusions when researchers have commercial ties shows how easily interpretations can be manipulated, leading to biased

treatment recommendations. As the authors of this study point out, this documented discordance shows that the peer review process fails to provide stringent enough safeguards against bias.

The APA's most recent practice guideline for major depressive disorder provides another example of how commercial ties with drug firms can bias the interpretation of meta-analyses. Elsewhere we reported[37] that two meta-analyses, both of which were published in high-impact medical journals and received international media attention, independently concluded that, because of a lack of demonstrated efficacy, antidepressant medication should not be the first-line intervention for mild to moderate depression.[38] In 2008, Irving Kirsch et al. concluded: "Drug-placebo differences increased as a function of initial severity, rising from virtually no difference at moderate levels of initial depression to a relatively small difference for patients with very severe depression, reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category."[39] In a 2010 patient-level meta-analysis, which is even more robust than a group-level one, Fournier et al. found that "[t]rue drug effects (an advantage of [antidepressant medications] over placebo) were nonexistent to negligible among depressed patients with mild, moderate, and even severe baseline symptoms…. [E]fforts should be made to clarify to clinicians and prospective patients that whereas [antidepressant medications] can have a substantial effect with more severe depressions, there is little evidence to suggest that they produce specific pharmacological benefit for the majority of patients with less severe acute depressions."[40]

However, the authors of the APA's practice guideline for depression interpreted the meta-analyses quite differently. They recommend antidepressants as a front-line intervention for mild to moderate depression, stating: "Response rates in clinical trials typically range from 50-75% of patients, with some evidence suggesting greater efficacy relative to placebo in

individuals with severe depressive symptoms as compared to those with mild to moderate symptoms."[41] This statement and their recommendation of pharmacotherapy obscures and misstates the main finding of both reviews of the literature; namely, that antidepressants were effective only for the most severely depressed patients and thus should not be the front-line recommendation for patients who are mildly or even moderately depressed. Is it a coincidence that all of the authors of this guideline had significant financial ties with drug firms and the majority served on speakers bureaus for the manufacturers of antidepressants? (Industry insiders refer to individuals who participate as speakers as "Key Opinion Leaders" because they are seen as important to the marketing of drugs and diseases.)[42]

In contrast to the APA's clinical practice guidelines, guidelines for depression produced by independent (versus industry-tied) organizations reached a very different conclusion about the harm-benefit ratio of antidepressants. For example, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom[43] and recent Dutch guidelines[44] for depression incorporate these recent meta-analyses to support the explicit recommendation that antidepressants should *not* be the first-line treatment for mild to moderate depression. This inconsistency between the APA's guidelines and the literature on which it is supposedly based raises questions about the trustworthiness of guidelines developed by individuals or organizations with ties to drug companies.

Transparency's Iatrogenic Effects

Although many researchers initially embraced academic-industry partnerships as a practical means by which science could advance, especially as government funding of research steadily declined, these relationships can undermine credibility and lead to the production and

dissemination of biased research. Many researchers believed that increased and mandatory transparency of commercial ties would preclude bias and ensure the trustworthiness of research studies and clinical guidelines. For example, in response to practices such as ghostwriting, overstating efficacy, and underreporting harms, the International Committee of Medical Journal Editors developed a set of recommendations for disclosure of authors' industry ties and for enhanced accountability.[45] In turn, government agencies, institutions, and medical specialty groups that produced guidelines developed policies that required transparency of commercial ties.

Unfortunately, Supreme Court Justice Louis Brandeis[46] was wrong: sunlight is not always the best disinfectant. Disclosure is an insufficient strategy for mitigating bias because bias does not result from the *concealment* of financial ties but from their *effects*.[47] Transparency thus "shifts the problem from one of 'secrecy of bias' to 'openness of bias.'"[48]

The inadequacy of transparency as a solution to psychiatry's dependency corruption is demonstrated by the continued controversies over the validity of diagnostic additions and revisions and by questions about the trustworthiness of pharmacotherapy treatment recommendations. It is also made evident by the recently published 2013 "Dollars for Docs" list of large payments from drug firms to U.S. clinicians. The investigative journalism group Propublica released the names of 22 physicians who had earned more than $500,000 from pharmaceutical companies since 2009 through speaking fees and consulting. Psychiatrists dominate the list; 12 of the 22 were psychiatrists, the top recipient being a psychiatrist who had earned over a million dollars.[49]

Moreover, there are often unintended consequences of transparency, and it may inadvertently increase bias.[50] Social psychologists such as George Loewenstein and Jason Dana

have demonstrated that when individuals disclose a competing interest, they give even more biased advice. Two compelling explanations that have been posited are referred to as *discounting* and *moral licensing*. In the former, individuals try to make up for the fact that their disclosures may cause others to discount or downplay their advice. In the latter, it is as if disclosure frees the individual to give even more biased advice because others have been warned (what has been referred to as the "caveat emptor" effect[51]). There is also a signal-to-noise problem when researchers and authors list every affiliation—even non-industry ones—so that the reader does not know how to evaluate the financial associations being reported. Thus, evidence suggests that transparency as a solution to conflict of interest is not only insufficient but may further complicate ethical decision-making.

What Do Informed Consent and Evidenced-Based Medicine Mean in an Age of Big Pharma?

Organized psychiatry's dependency corruption—together with documented industry practices such as ghostwriting, the selective reporting of clinical trials, and variability in the reporting of harm-related results of randomized clinical trials[52]—complicates collaborative decision-making between patients and health care providers. Informed consent requires an assessment of the risks and benefits of the proposed treatment, knowledge of the alternatives to the proposed treatment, and disclosure of information that would affect decision-making. The original developers of informed consent practices, however, could not have anticipated the prevalence of collaboration between academic organizations and the pharmaceutical industry. How meaningful can informed consent be if mental health practitioners themselves are unaware of reliability and validity

problems in the *DSM* and do not receive accurate and complete data on the efficacy and risks of psychotropic medications in practice guidelines?

The conceptual framework of institutional corruption[53] highlights the myriad ways in which medical evidence is corrupted, well before pharmaceutical representatives attempt to market medications to physicians. Specifically, (a) the failings of the peer-review process to adequately protect against ghostwriting and (b) the documented discordance between results and conclusions (such that the conclusions support the sponsoring company's drug, even if the results do not) make it difficult for the prescriber to be adequately informed about the evidence base for new drugs. This, in turn, undermines genuine informed consent and collaborative decision-making. There have been glaring examples of iatrogenic harm caused by the distortion of important information about a drug's adverse side effects.[54]

In light of the corruption of the evidence upon which clinical decision-making is based, informed consent can no longer be seen as a scripted and static event, achieved by a simple listing of currently known risks, benefits, and alternatives. Rather, we need a dynamic model of informed consent.[55] It should be a conversation that occurs over time,[56] encouraging both doctors and patients to think critically about the scientific evidence. Patients and clinicians should be made aware of the dependency corruption that results from academic-industry relationships and the economies of influence—such as the APA's guild interests and the alliance among the FDA, drug companies, and organized psychiatry—that sustain this corruption.

Patients and doctors need to know that only 11 to 14 percent of all new drugs approved by the FDA show a clinically relevant benefit over existing treatments[57] and that the percentage of drugs showing no significant improvement has increased in the last decade, as has the percentage of drugs with a *negative* harm/benefit ratio (more harm than benefit).[58] Patients and

doctors should also know that pharmaceutical companies fund most of the research on the efficacy and safety of new medications and that these studies can only assess a medication's short-term effects, both positive and negative.

Additionally, mental health clinicians need to take a critical approach to contemporary models of psychiatric taxonomy and treatment. Professional training usually teaches the clinician to learn new content, such as new the diagnostic criteria in the *DSM*-5 or the benefits of a new antidepressant. But because pharmaceutical companies provide substantial financial support for continuing medical education (CME)[59] sometimes underwriting it entirely—CME has become compromised by another corrupting economy of influence. The idea of evidence-based medicine and informed consent are compromised when the peer-review process fails to provide enough of a safeguard against systemic practices that favor commercial interests (such as the use of secondary endpoints to generate a positive result of drug over placebo).

Not only should dependence on industry funding of CMEs be eliminated, but critical thinking and de-biasing strategies should be a required part of postgraduate medical training. Instead of focusing only on content-related issues, CME should include courses and activities that review the empirical literature on the funding effect and its implications for assessing the trustworthiness of diagnostic and clinical guidelines. Mental health clinicians need CME that helps them critically evaluate research on the efficacy and safety of psychotropic medications. For example, reporting response rates (or a decrease in symptoms that are statistically significant but not clinically meaningful) rather than statistics on remission in randomized controlled trials for antidepressants artificially inflates the benefits of antidepressant medication. Insofar as all medical decisions are made under conditions of uncertainty,[60] informed consent practices will be enhanced by training practices that strengthen the decision-making process.

Conclusion

Shifting the focus from an individual model of quid pro quo corruption to the conceptual framework of institutional corruption reveals the systemic nature of psychiatry's "crisis of credibility." Addressing this crisis has epistemic, ethical, and public health implications. The distortion of the science underlying psychiatric diagnostic and treatment guidelines can result in significant social injury (that is, overdiagnosis and overtreatment). If "evidence-based medicine" is to have genuine meaning in organized psychiatry, calls for disclosing or managing individuals' financial conflicts of interest must be recognized as ineffective and potentially harmful. It is dependency corruption that undermines evidence-based medicine and informed consent and normalizes the promotion of industry interests.

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