Dynamic Informed Consent Processes Vital for Treatment with Antidepressants

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Dynamic informed consent processes vital for treatment with antidepressants

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Abstract

Advances in technology and transparency have greatly accelerated the ability of clinicians to remain current with regards to being informed and informing patients about the risk/benefit ratio when considering antidepressant medication. In spite of this, the current climate of pharmaceutical industry influence on medical practice does much to hinder informed consent processes. Recent findings of previously unknown and potentially dangerous adverse effects of the second- and third-generation classes of antidepressants underscore the importance of enhancing the practice of informed consent. After considering the concept of informed consent as it has evolved over time, the authors summarize some of the newer side effects associated with second- and third-generation antidepressants and then move on to describe impediments in the way of achieving adequate informed consent at the clinical encounter. Among these impediments, the authors discuss the impact of industry influence, cognitive bias in decision-making, and time constraints. These obstacles and the notion that modern antidepressants are not as safe as once thought offer an opportunity to revisit the process of informed consent. A dynamic concept of informed consent is proposed with the acknowledgement that a mere listing of side effects or pro forma approach to informed consent is inadequate, and that a deep and ongoing conversation with patients will more likely result in patient empowerment and a strengthening of the therapeutic alliance. This process is analogized to an “n=1” approach where patients’ idiosyncratic responses to second- and third-generation antidepressants can be used to update prior beliefs based on large-scale trials and allow patient and doctor to shoulder the burden of uncertainty together, thereby enhancing placebo and minimizing nocebo response and leading to more optimal treatment outcomes.
Introduction

Over the last few decades, evidence-based approaches to the management of psychiatric disorders have incorporated the concept of concordance or shared decision-making between clinicians and patients (Appelbaum & Grisso, 1997; Deegan & Drake, 2006; Penston, 2007). As a result the paradigm has shifted from a paternalistic model, where the clinician makes decisions for patients, to a patient-choice model. However, the prevalence of academic-industry collaborations, the dramatic increase in industry-funded research, the financial ties between prescribing providers, organized medicine, and the pharmaceutical industry, and the rise of psychopharmacology as the predominant intervention in psychiatry have complicated, and in some ways compromised, the informed consent process. For example, there is evidence of attempts by some pharmaceutical companies to influence vital information regarding efficacy and safety studies in high ranking medical journals through practices such as ghost writing and selective reporting of clinical trials and outcomes. In addition, there is documented variability in the reporting of harm-related results in publications of randomized controlled trials (Howland, 2011; Pitrou, Boutron, Ahmed, & Ravaud, 2010; Spielmans & Parry, 2010). Despite these clearly unethical practices, the problem most often “is not venality or intentional deception…. The problem is that bias can so easily be introduced unintentionally” (Avorn & Choudhry, 2010, p. 2233). As a result, the published literature may not fully capture a balanced view of the risk/benefit ratio for commonly prescribed psychotropic medications such as antidepressants.

The fact that clinicians may be receiving imbalanced and perhaps inaccurate or biased information about the side effect profiles of newer antidepressants is particularly problematic in light of the rise in antidepressant use. A recent Center for Disease Control report announced that there has been a 400% increase in the use of antidepressants since 1988; currently over twenty-
seven million people in the United States are taking antidepressants. In addition to being the standard treatment for depressive disorders, antidepressants are increasingly being prescribed for other conditions such as chronic daily headache, back pain, neuropathy, sleep-related conditions, fatigue, anxiety spectrum disorders (e.g., social anxiety disorder and panic disorder), adjustment disorders, eating disorders, fibromyalgia, and hot flashes. This widening range of use may be driven in part by the longstanding perception that modern antidepressants are extremely safe. However, recent research has shed a more sobering light on the actual safety and tolerability profiles of second- and third-generation antidepressants. Policy makers, bioethicists, and health care professionals are thus in full agreement that providers need to “integrate information about medical risks of serotonergic antidepressants into their clinical decision-making, informed consent process, baseline assessment, and follow-up monitoring” (Looper, 2007: 7; see also Bahrick & Harris, 2008).

Despite the concern that these data have generated, however, it seems that clinical practice has yet to adapt. A recent study demonstrated that in only 1.5% to 2% of clinical sessions did psychiatrists discuss the issue of adverse effects with their patients after initiating treatment with an antidepressant (Linden & Westram, 2011). Moreover, informed consent is hardly mentioned in the American Psychiatric Association's clinical practice guidelines for the treatment of Major Depressive Disorder (American Psychiatric Association, 2010).

The recent discoveries of new and potentially dangerous adverse effects of antidepressants, along with the compromised state of informed consent practice, warrant a reappraisal of the informed consent process regarding these common medications. In this article, after considering the concept of informed consent as it has evolved over time, the authors review the adverse effects associated with second- and third-generation antidepressants and then move
on to discuss various impediments to the informed consent process, such as the influence of the pharmaceutical industry on the information available to prescribers and its quality, cognitive biases in decision making, and the widespread conceptualization of informed consent as a single action. The authors conclude by reframing informed consent as a dynamic rather than a pro forma process that involves approaching antidepressant prescription empirically and collaboratively, allowing doctor and patient to manage uncertainty together within the treatment alliance and leading to more optimal treatment outcomes.
Informed consent: A brief history and context

As Beauchamp (2011) noted, although the term ‘informed consent’ emerged in the 1950s, serious discussion about the meaning of informed consent, particularly in terms of the patient’s or research participant’s perspective (i.e., his/her actual understanding of the information being disclosed), did not receive serious attention until the 1970s. The concept of informed consent as it applies to research was first formally defined by the Nuremberg Code in 1947 and continued to be updated over time by various organizations, including the World Medical Association in Helsinki in 2004 (http://ohsr.od.nih.gov/guidelines/helsinki.html). Over time the concept of informed consent in clinical practice evolved as well and came to signify “the disclosure of important information so that a patient may be able to assess the risks and benefits of the proposed treatments and understand the alternatives to the proposed treatment” (see e.g., Bursztajn, Feinbloom, Hamm, & Brodsky, 1990; Gutheil, Bursztajn, & Brodsky, 1984).

Although there are different standards for disclosure, such as the professional practice standard, which focuses on the question of the customary practices of the profession, it is the reasonable patient standard that is used most frequently in the United States as the required threshold for disclosure. This standard, derived from the landmark Canterbury v. Spence federal court ruling, can be stated as following: “What would a reasonable patient want to know with respect to the proposed therapy and the dangers that may be inherently or potentially involved” (Canterbury v. Spence, 464 F.2d 772, 1972). A risk is considered material when a reasonable person, in what the physician knows or should know to be the patient’s position, would be likely to attach a significance to the risk or cluster of risks in deciding whether or not to forego the proposed

therapy\textsuperscript{2,3} (Cantebury v. Spence, 464; Foy v. Greenblott, 141 Cal. App. 3d. 1, 9, 1983; Mathis v. Morrissey, 11 Cal. App. 4th 332 [13 Cal. Rptr. 2d 819], 1992). In 2003, a review (Mazur) noted that the reasonable patient standard for informed consent was gaining currency not only in the United States but also internationally, in Canada, Great Britain, and Australia. This trend has continued to date and given the globalization of clinical trials is likely to continue. Moreover, given the adoption and usage of a variety of “universal” human subject protection codes on the heels of the Nuremberg trials, the international influence of the reasonable patient standard for informed consent is likely to grow.

Despite these major legal rulings, the emergence of an entire field of bioethics, and the proliferation of literature on the topic of informed consent, the practice of making sure that one obtains meaningful informed consent “has been slow to conform to abstract theory” (Beauchamp, 2011, p.517). Moreover, the concept of informed consent was developed when medical information was far more static and trust in biomedicine and regulatory bodies was taken for granted. The framers of informed consent practices could not have anticipated an information age in which advances in technology allow immediate and public access to emerging data regarding drug efficacy and side effects. Nor could they have anticipated the prevalence of collaborations between academic organizations and the pharmaceutical industry—collaborations that have raised real questions about how meaningful the informed consent process can be if practitioners are not privy to accurate and complete data on efficacy and risks of medications.

\footnote{Foy v. Greenblott, 141 Cal. App. 3d. 1, 9, 1983.}
\footnote{Mathis v. Morrissey, 11 Cal. App. 4th 332 [13 Cal. Rptr. 2d 819], 1992.}
In order to respect patient autonomy, the informed consent process must begin with physicians who have a clear understanding of the risks and benefits inherent in prescribing a medication as well as how various alternatives fare in comparison. In today's industry-dominated climate, marketing and publishing tactics utilized by drug companies make it difficult for the prescriber to be adequately informed. Indeed, the field of medicine has had to contend with some glaring examples of iatrogenic harm caused by the distortion of important information about a drug’s adverse effects. Merck’s blockbuster drug Vioxx (Rofecoxib), which nearly doubled the risk of myocardial infarction and stroke (Bresalier et al., 2005; Avorn & Choudhry, 2010), is perhaps the most well-known case. As a result of this and other high profile cases, providing genuine informed consent has become a critical public health issue for all medical subspecialties. We therefore proceed with a survey of some of the known adverse effects of the second- and third-generation antidepressants.
Side effects and adverse events

Post-market monitoring of second- and third-generation antidepressants has called into question the perception that they are mostly safe. Recent meta-analyses and reviews of safety and tolerability information of clinical trials provide the bulk of data underlying this concern (see Table 1: Summary of side effects and adverse events associated with second- and third-generation antidepressants). For example, in an updated meta-analysis, Gartlehner et al. (2011) found that 63% of patients reported at least one adverse event during the course of treatment and that discontinuation rates between selective serotonin reuptake inhibitors (SSRIs) and other second-generation antidepressants were generally similar. Of note is that due to the size and length of most trials, the authors conclude that comparative risk across drugs for serious adverse events other than sexual dysfunction (i.e., suicidality, cardiovascular events, hyponatremia, seizures, hepatotoxicity, and serotonin syndrome) could not be determined. Since such clinical trials cannot sufficiently capture the less common but more serious adverse events, the United States Food and Drug Administration (FDA) depends on post-market surveillance in order to detect and respond to these events (Wolfe, 2012).

One serious adverse event that does appear in clinical trials is sexual side effects. Montejo-Gonzalez et al. (1997) found that over 50% of subjects taking an SSRI experienced some type of sexual dysfunction, with decreased libido and delayed orgasm being the most common. Clayton, Keller, and McGarvey (2006) note that even for patients who do not qualify for global sexual dysfunction, 96% of female patients and 98% of male patients taking SSRIs experience dysfunction in at least one sexual phase. Seidman (2006) noted that at least 25% of men taking SSRIs experience delayed ejaculation. This phenomenon is likely underreported, as the correlation between SSRIs and delayed ejaculation in men is not well-researched.
Other SSRI side effects continue to be discovered. Recent reports suggest that SSRIs increase the risk of upper gastrointestinal (GI) tract bleeding (Dalton, Sørenson, & Johansen, 2006; de Abajo, Montero, Rodriguez, & Madurga, 2008; Loke, Trivedi, & Singh, 2007) and pose particular problems for the elderly, including increased risk for falls, bone fractures (Hermann 2000; Richards et al., 2007), and hyponatremia (Movig, 2002), and a possible effect on intraocular pressure for those at risk for glaucoma (Costagliola, Parmeggiani, & Sebastiani, 2004). Ziere et al. (2008) found that SSRI use more than doubles the risk of nonvertebral fracture, with the risk increasing in those taking an SSRI for more than six months. Weight gain associated with SSRI use (Fava, 2000) has led to concerns about increased diabetes risk with long-term use (Andersohn, Schade, Suisse, & Garbe, 2009). Haddad and Dursun (2008) also note the increased risk of serotonin toxicity and discontinuation syndrome in patients treated with SSRIs. Rarely, suicidality is also associated with antidepressant use (Reeves & Ladner, 2010), with some evidence of increased risk with SSRIs relative to tricyclic antidepressants (TCAs) (Fergusson et al., 2005; Gunnell, Saperia, & Ashby, 2005).

In addition, studies have documented adverse neonatal outcomes in relation to maternal exposure to SSRIs and other newer serotonergic/noradrenergic antidepressants from the last trimester through delivery, including mild central nervous system, motor, respiratory, and GI signs and metabolic dysfunction (see Tuorri et al., 2009 for review) as well as cardiovascular defects (Diav-Citrin et al., 2008; Louik, Lin, Werler, Hernandex-Diaz, & Mitchell, 2007) and a risk of persistent pulmonary hypertension (Chambers et al., 2006).
Progress in the field of pharmacodynamics has led to increasing concerns about the complex relationships among serotonin, SSRIs, certain TCAs, prolactin, and tamoxifen, and how these inter-relationships affect both pharmacodynamics and cancer risk (Kelly et al., 2010). Some antidepressants, especially SSRIs, are potent inhibitors of the cytochrome P450 monooxygenase enzymatic system (a system that metabolizes antineoplastic as well as other agents). Thus, antidepressants may directly enhance tumor cell proliferation as suggested by the expanding biological and clinical research on cytochrome P450 enzymes and the deleterious effects of these enzymes on the metabolism and therapeutic efficacy of tamoxifen and other antineoplastic agents (Spina et al., 2008; Aubert et al., 2009). In fact, researchers found an increased risk of death from breast cancer in 630 women taking paroxetine while receiving tamoxifen therapy (Kelly et al., 2010). Moreover, women treated with tamoxifen who were also treated with a moderate to potent cytochrome P2D6 inhibitor (fluoxetine, paroxetine, or sertraline) were found to have an increased risk of a breast cancer recurrence compared to women taking no SSRI (Aubert et al., 2009), although it should be said that in another study researchers did not observe an elevated risk of breast cancer recurrence in women treated with antidepressant inhibitors of cytochrome P2D6 (Azoulay, Dell’Aniello, Huiart, Galbaud du Fort, & Suissa, 2011).

In sum, although the more recent findings regarding adverse events are preliminary, they raise significant questions about the safety and tolerability of second- and third-generation antidepressants and prompt a revisiting of the informed consent process for this class of drugs. Drugs once considered to be safe and tolerable, with sexual dysfunction and GI discomfort thought to be their primary adverse effects, are now suspected to carry serious risks such as gastrointestinal bleeding and an increased risk of fractures. This problematic situation is further
complicated by marketing practices distorted by financial conflicts of interest and places a heavy burden of responsibility on clinicians to avoid pitfalls and manage uncertainties within the process of informed consent so that patient autonomy will not be compromised.
Communicating the emerging data on side effects: Toward a more genuine informed consent process

Industry plays a dominating role in psychopharmacological education (Brodkey, 2005; Gagnon & Lexchin, 2008), and there is increasing documentation that the evidence base gets distorted as a result of these partnerships (Friedman & Richter, 2004). It is noteworthy that the financing for educational/promotional activities of pharmaceutical companies are derived from their marketing and administrative budgets (Brodkey, 2005). It is therefore important for prescribers to be mindful of pharmaceutical marketing strategies and to actively seek information from independent sources (e.g., the Cochrane Central Register of Controlled Trials and MedWatch, the FDA website for updated reporting of safety information and adverse events) rather than relying on updates regarding the risks and benefits of any given medication from an industry-sponsored source (Applbaum 2009; Shaughnessy, Slawson, & Bennett, 1994; Spielmans & Parry, 2010).

Semantic decision-making biases often combine with marketing strategies to form another potential pitfall on the way to genuine informed consent (Bursztajn et al., 1991; Bursztajn, Chanowitz, Gutheil, & Hamm, 1992). For example, warnings and contraindications buried in the “adverse events” section of the labeling of a pharmaceutical product are not likely to be remembered as well as the indications and benefits that are prominently promoted. Moreover, the consequences of automated thinking (Hamm, 2009b) and the “irrational persistence in belief” (Hamm, 2009a) may be reinforced by delays in disclosing adverse effects of medications. Many clinicians have internalized the belief that second- or third-generation
antidepressants are always the treatment of choice. Once such automatic prescribing habits set in they become difficult to dislodge. Additionally, industry promotion can subtly—but powerfully—frame the questions clinicians ask. For example, the “newer is better” bias encourages questions such as “Which among this new class of drugs is better than the others?” rather than "How are these new drugs any better than older drugs or alternative treatments?"

In order to facilitate collaborative decision-making, it is important for clinicians not only to review independent sources of information for emerging safety and efficacy data, but also to initiate conversations with their patients about these new data. It is helpful to communicate to patients that it is indeed difficult to make sense of all of the information they hear and read about regarding their psychotropic medications (e.g., in direct-to-consumer advertising campaigns, news stories, etc.). Evidence suggests that prescribing physicians vary in their beliefs about what constitutes an adequate level of knowledge disseminated to patients about relative benefits and harms of treatments (Larkin, Clifton, & de Visser, 2009; Laugharne, Davies, Arcelus, & Bouman, 2004). Instead of adopting a “don’t ask, don’t tell” policy, it is recommended that clinicians specifically invite patients to voice any and all concerns about a medication’s side effects or lack of effectiveness (Cosgrove & Bursztajn 2007). The clinician who is proactive and takes care to inform patients during the course of treatment about newly emerging data is more likely to enhance a trusting relationship and therapeutic alliance than one who avoids difficult dialogues.

Emerging evidence on antidepressant side effects and efficacy also invite a shift in attitude regarding the prescription of antidepressants from standardized to empirical. There is an argument to be made that updated data on the variable efficacy of antidepressants in treating
mild to moderate depression (Fournier et al., 2010) have transformed American Psychiatric Association guidelines recommending standard treatment into an investigative process for each individual patient. With increasing applicability of the reasonable person standard as outlined earlier, this shift would necessitate the tactful updating of patients who previously believed that their treatment was standard with the information that their treatment is empirical and in effect, a one-person experiment.

In this spirit, and rather than being bound solely by statistics culled from studies involving large numbers of subjects, we suggest that clinicians adopt an “n=1” attitude to the weighing of risks and benefits with patients. Average rates taken from studies will of course inform our prior probabilities of adverse events and initial conversations with patients, but the informed consent process is best conceptualized as a collaborative journey where both benefits and side effects are continually updated for each individual patient. This is particularly important in light of data suggesting that the presence of mental illness can complicate a patient’s response to medications and may result in intolerance or even the experience of rare side effects (Davies, Jackson, Ramsay, & Ghahramani, 2003), and moreover that idiosyncratic reactions to SSRIs abound, with outcomes from any single medication trial often being unpredictable (Berndt, Bhattacharjya, Mishol, Arcelus, & Lasky, 2002).

These waters of uncertainty suggest a larger role for the informed consent process itself as a conduit for treatment. By initiating a conversation with patients that includes not just frequent psychoeducation and provisions for close monitoring, but also an exploration of patients’ expectations and the meaning of medications as it relates to their identity and suffering, physicians may be able both to enhance placebo and minimize nocebo effects that are typical of
pharmacologic treatment of depression (Fournier et al., 2010). A dynamic approach to informed consent can do much to distinguish pharmacology from mere pill-dispensing (Gopal, Pirakitikuir, & Bursztajn, 2005) and presents an opportunity to manage the ambiguity surrounding psychiatric illness within a healthy therapeutic alliance (Gutheil et al., 1984).
Conclusion

Clinicians today practice in a time-limited, pharmaceutical-industry dominated climate in which reductive biological models are heavily promoted. Such models reinforce an acontextual view of patients’ problems and a disease- rather than patient-centered model of care. As a result, “diagnosis by checklist” (Andreasen, 2007) becomes a primary source of automatic prescribing (Cosgrove & Bursztajn, 2007). Thus, genuine informed consent requires, first and foremost, that mental health professionals adopt a mindful approach to psychiatric taxonomy and be aware not only of the uses, but also the limitations of and alternatives to psychopharmacological interventions. Respecting patient autonomy requires that clinicians be aware of the marketing practices and biases that may distort their appraisal of the relative risks and benefits of medications such as antidepressants, and moreover that they consider the ways in which people can be manipulated by social constructions of normalcy and health in an industry-dominated climate (see e.g., Ells, 2003). This increasingly complex network of considerations presents distinct challenges for clinicians, but dynamic informed consent processes offer a way to acknowledge the uncertainty associated with antidepressants while simultaneously empowering patients in their recovery from illness.
References


Davies, J. C., Jackson, P. R., Ramsay, L. E., & Ghahramani, P. (2003). Drug intolerance due to nonspecific adverse effects related to psychiatric morbidity in hypertensive patients. *Archives of Internal Medicine, 163*(5), 592-600.


Table 1: Summary of side effects and adverse events associated with second- and third-generation antidepressants

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year of Publication</th>
<th>Study Type</th>
<th>Results</th>
<th>Side Effect Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentejo-Gonzalez</td>
<td>1997</td>
<td>Prospective cohort study</td>
<td>Over 50% of participants experienced some sexual dysfunction. Sexual dysfunction varied across SSRIs and was positively correlated with dose.</td>
<td>Sexual</td>
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<tr>
<td>Clayton</td>
<td>2006</td>
<td>Cross-sectional observational study</td>
<td>95.6% of women and 97.9% of men who do not qualify for global sexual dysfunction experience sexual dysfunction in at least one phase.</td>
<td>Sexual</td>
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<td>Dalton</td>
<td>2006</td>
<td>Review</td>
<td>Evidence for a causal role of</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Findings</td>
<td>Special Populations</td>
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<tr>
<td>De Abajo</td>
<td>2008</td>
<td>Review</td>
<td>Evidence for increased risk of upper GI bleeding with SSRI use. Risk is increased for elderly and concomitant use of NSAIDs.</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Loke</td>
<td>2007</td>
<td>Systematic review</td>
<td>Use of SSRIs alone and with NSAIDs increases the risk of upper GI bleeding.</td>
<td>Gastrointestinal</td>
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<tr>
<td>Herrmann</td>
<td>2000</td>
<td>Review</td>
<td>Potential adverse events of falls, hyponatremia, weight loss, sexual dysfunction, and drug interactions.</td>
<td>Special populations: elderly</td>
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<td>Richards</td>
<td>2007</td>
<td>Prospective cohort study</td>
<td>Associated with increased risk for bone fracture and</td>
<td>Osteo; Special populations: elderly</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Findings</td>
<td>Population</td>
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<tr>
<td>Movig</td>
<td>2002</td>
<td>Case-control</td>
<td>Increased risk of hyponatremia when compared with other classes of antidepressants; more common in elderly patients.</td>
<td>Metabolic; special populations: elderly</td>
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<td>Costagliola</td>
<td>2004</td>
<td>Review</td>
<td>Relationship between SSRI use and changes in intraocular pressure, especially for elderly.</td>
<td>Special populations: elderly</td>
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<td>Ramasubbu</td>
<td>2004</td>
<td>Systematic review</td>
<td>Very low rates of cerebrovascular adverse events exist, including intracranial hemorrhage, disease, and vasoconstrictive stroke.</td>
<td>Cerebrovascular</td>
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<td>Ziere</td>
<td>2008</td>
<td>Prospective cohort study</td>
<td>Risk of nonvertebral fractures with</td>
<td>Special populations: elderly;</td>
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<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Findings</td>
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<tr>
<td>Fava</td>
<td>2000</td>
<td>Review</td>
<td>Use of SSRIs as a class are associated with weight gain.</td>
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<td>Andersohn</td>
<td>2009</td>
<td>Case-control</td>
<td>Risk of diabetes mellitus increased with long-term use of SSRIs and tricyclic antidepressants.</td>
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<td>Haddad</td>
<td>2008</td>
<td>Review</td>
<td>Risk of serotonin toxicity, decreased seizure threshold, and neurological symptoms of discontinuation syndrome.</td>
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<td>Reeves</td>
<td>2010</td>
<td>Review</td>
<td>Evidence supports the rare occurrence on antidepressant-induced suicidality.</td>
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</table>

SSRI use, particularly prolonged use.

Musculoskeletal

Endocrine

Neurological
<table>
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<tr>
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<th>Year</th>
<th>Study Type</th>
<th>Findings</th>
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<td>Fergusson</td>
<td>2005</td>
<td>Systematic review</td>
<td>Association between SSRI use and suicide attempts when compared to placebo and non-TCA antidepressants.</td>
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<td>Gunnell</td>
<td>2005</td>
<td>Meta-analysis</td>
<td>Some evidence for increased risk of self-harm and moderate risk of suicidal thoughts.</td>
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<td>Tuccori</td>
<td>2009</td>
<td>Review</td>
<td>Association between maternal exposure and persistent pulmonary hypertension and self-limiting neonatal behavior syndrome in infant. Possible increased risk of miscarriage and other neonatal risks require Special populations: pregnancy</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Study Type</td>
<td>Findings</td>
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<tr>
<td>Diav-Citrin</td>
<td>2008</td>
<td>Prospective cohort</td>
<td>Exposure to fluoxetine in first trimester associated with cardiovascular anomalies in newborns.</td>
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<td>Louik</td>
<td>2007</td>
<td>Case-control study</td>
<td>Some SSRIs may increase risk of certain cardiovascular defects in infants when used in first trimester.</td>
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<tr>
<td>Chambers</td>
<td>2006</td>
<td>Case-control study</td>
<td>Association between use of SSRIs in late pregnancy and risk of persistent pulmonary hypertension in the infant.</td>
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<tr>
<td>Kelly</td>
<td>2010</td>
<td>Population-based cohort study</td>
<td>Concomitant use of paroxetine and tamoxifen association with increased risk of</td>
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<tr>
<td>Author</td>
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<td>Study Type</td>
<td>Description</td>
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<td>Spina</td>
<td>2008</td>
<td>Review</td>
<td>Second-generation antidepressants differ in their potential to interact with other medications.</td>
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<tr>
<td>Aubert</td>
<td>2009</td>
<td>Retrospective cohort study</td>
<td>Clinically significant interaction between tamoxifen and CYP2D6 inhibitors, which includes some second-generation antidepressants.</td>
</tr>
</tbody>
</table>