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Review

Fact: Antidepressants and anxiolytics are not safe during pregnancy

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Abstract

Psychotropic medication is used by a growing number of women of reproductive age. Although necessary in some cases, in many others non-pharmacological treatments offer valid alternatives for the pregnant woman. The noxious effects of antidepressants and anxiolytics urge the physician to look for other solutions. The efficacy of alternative treatment is enhanced by early detection that requires monitoring for mood disorders from the earliest stages of pregnancy, and multidisciplinary professional care.

Keywords: Psychotropic medication; Antidepressants; Benzodiazepines; Depression; Anxiety; Pregnancy; Malformation; Multidisciplinary care

Contents

1. Repeated recent warnings against antidepressants and anxiolytics

Of late, medication use during pregnancy, and especially the use of antidepressants and anxiolytics, is being critically commented in scientific and government publications. Nevertheless, many reviews conclude that the established noxious effects of these drugs are not serious enough to limit their use. One of these relatively recent reviews typically concludes: ‘‘The body of evidence in the literature to date suggests that psychotropic drugs as a group are relatively safe to take during pregnancy (. . .)’’ [1]. However, recent evidence-based information on the two most commonly prescribed groups of psychotropic drugs, being antidepressants and benzodiazepine anxiolytics, does not support such optimism:

(1) In 2004 the U.S. Food and Drug Administration (FDA) already issued warnings that the use of antidepressants in the *last trimester* of pregnancy may cause serious problems for neonates, resulting in prolonged hospitalization, respiratory support, and tube feeding [2].

In October and December 2005 the FDA issued warnings that the use in *early pregnancy* of paroxetine (Paxil) may cause major congenital malformations [3].

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In July 2006 the FDA warned healthcare professionals of new findings, based on two studies, regarding the potential risks associated with both discontinuation and continuation of antidepressant therapy with selective serotonin reuptake inhibitors (SSRIs) during pregnancy [4]. Their continued use was linked to a six-fold increase in the risk for persistent pulmonary hypertension (PPHN) in newborns.

Recent independent studies confirm the FDA's warnings. A 2006 population study by Oberlander et al., $N = 119{,}547$, concerning the period 1998–2001, compared infants exposed to SSRIs with infants of depressed mothers, and found that the first group had significantly lower birth weight and gestational age; more infants born at less than 37 weeks, more neonatal respiratory distress, jaundice, and feeding problems [5]. A 2006 cohort study by Wogelius et al., $N = 150{,}780$, shows a 44% increase in congenital malformations when SSRIs were taken during early pregnancy, and a 100% increase when taken during the second or third month (adjusted relative risks 1.34 and 1.84, respectively) [6].

(2) Since 1984, benzodiazepines figure on the United Nations' list of dangerous drugs; their recommended use is limited to several weeks only. In the FDA rating system of medication during pregnancy (categories A, B, C, D and X) benzodiazepines are category D and X, thus are considered most dangerous, more so than opiates which are at B and C. The antidepressant paroxetine (Paxil) was recently moved from C to D. The rating system is currently under revision [7].

Studies indicate that babies exposed prenatally to benzodiazepines are at risk of the following:

- Lower birth weight.
- Lower Apgar scores.
- Poor neonate adjustment, such as
  - Breathing difficulties.
  - Floppy muscles.
  - Unstable body temperature.
  - Alteration in heart rate and function.
  - Altered EEG measurement.
- Withdrawal syndrome.
- Cot death.
- Malformation.
- Developmental difficulties.

The puzzling reality is that, though more evidence becomes available as to the possible and probable dangers of psychotropic medication for the pregnant woman and her child, many authors remain reluctant to admit that these substances are noxious enough to warn against their use. Some psychiatric conditions may require medication during pregnancy, but depression and anxiety in many cases do not. Authors often do urge the clinician to weigh pro's and contra's in each case, but too often antidepressants and benzodiazepines are presented as the only solutions available for the depressed or anxious pregnant woman, as if she must either take these drugs or suffer the consequences of untreated depression or uncontrolled anxiety. The accumulating and conclusive evidence as to the efficacy of non-pharmacologic alternatives such as psychological treatments has still to convince clinicians that depression and anxiety during pregnancy can in many cases be managed without medication.

2. The precautionary principle in medicine

Medication is not ''safe, until proven unsafe''. Neither does FDA-approval warrant a drug to be safe, not for authorized uses and even less for unauthorized uses. However, the patient is not necessarily aware of these distinctions, and the use of the term ''relatively safe'' in medical publications that are – in the internet age – available to the general public, adds to certain confusion. The recent paroxetine warnings come after a long period of time in which medical publications and reviews generally accepted ''antidepressants'', including this popular drug, to be safe for use during pregnancy [8]. Medical and ethical considerations warn against the use of substances that are possibly or probably noxious for the unborn or young child. The Precautionary Principle was formulated a decade ago as a guideline that can be summarized as follows: ''*When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically*'' (The Wingspread Statement, 1998) [9]. Environmental health specialists argue that there is every reason for medicine to adhere to the Principle's implications [10]. However, National Institute of Environmental Health Sciences studies show how the choice of research questions affects the potential of results to inform action, illustrating an all too prevalent and problematic scientific ''tunnel-vision'' that at times makes us study and compare second options whilst leaving available first options aside. Also, the pharmaceutical industry pushes for the medicalization of all distress.

Pregnancy is an especially sensitive condition where the Precautionary Principle should always be applied. In depression or anxiety, medication is not the only option. When several proven options are available, those that are harmless to mother and/or child should be actively promoted and preferred over questioned options. Never can we refer to psychotropic medication as ''safe'' in pregnancy, not even ''reasonably safe'', because studies prove differently and, moreover, neither patients nor doctors have sufficient information to take a truly balanced risk-benefit decision. The physician, therefore, must provide all available information and options to the patient and thus share the responsibility for what constitutes a reasonable risk, leaving the final decision with the informed patient.

3. Benzodiazepines associate with malformations, but does not stress associate with miscarriage?

The 2005 revision quoted earlier still alleges: ‘‘There is insufficient evidence to prove that benzodiazepines are human teratogens’’ [1]. Similar statements are to be found in very recent publications [25]. This suggests that the authors consider the use of probably dangerous drugs justified until *proven* to cause major malformations. A more prudent attitude would require that the clinician, when considering prescribing benzodiazepines in pregnancy, weighs the existing evidence that argues against taking the risks as spelled out by a considerable body of scientific evidence in order to decide whether in this particular case exposure to those risks are justified. For instance, another 2005 study reviewed the evidence linking miscarriage to stress and finds it lacking [11]. However, high levels of cortisol in the first month of pregnancy do relate to miscarriage, although this fact escapes normal clinical controls that do not start until the 6th week. Thus, there is no hard evidence that stress during pregnancy must be treated on account of an increased risk of miscarriage, whereas treating stress with benzodiazepines does present an increased risk to the child.

In a similar venue as the 2005 revision cited above, a 1998 meta-analysis by a group of Canadian pharmacists considered that benzodiazepines do not offer a major threat to infant integrity [12]. Interestingly, their analysis proved that the better-controlled studies do reveal a significantly increased risk for major malformations due to benzodiazepine use. The authors however disregarded that mathematical piece of information to conclude, ‘‘. . . benzodiazepines do not seem to be major human teratogens, but because some cases of cleft lip can be visualized by fetal ultrasound level 2 ultrasonography should be used to rule out this malformation’’. These conclusions only raise more questions. What should be considered ‘‘major’’ human teratogens? Do ‘‘minor’’ human teratogens qualify as acceptable treatment options during pregnancy? Even when other options with confirmed efficacy are at hand? In any case, considering its psychological consequences, cleft lip remains an important malformation and though it can be detected by ultrasound, this would only confirm the problem, but not rule it out nor cure it.

British medical authorities, such as the Committee on the Safety of Medicines, are uniform in their warnings to avoid benzodiazepines in pregnancy and lactation [13]. Many studies on the teratogenic effects of these drugs recognize that the hospital records that were studied *do not reflect the reasons for early voluntary cessation of pregnancies*. In other words, those abortions that were sought for (suspected) malformations would go unnoticed or at least unrecorded, for reasons of privacy. Long-term effects of benzodiazepine use in pregnancy have not been adequately studied, but many studies confirm the noxious short, medium and long term effects of benzodiazepines in humans, notably so in the elderly [14,15] but also in (very fit) astronauts [16].

4. Alternatives to antidepressants and benzodiazepines

Psychotherapy has been shown to be as effective as antidepressant therapy and more effective than usual care in the management of patients with mild to moderately severe depression [17–19]. Psychotherapy has shown to be as effective as pharmacotherapy in the treatment of anxiety disorders [20]. Other proven alternatives comprise breast-feeding, exercise, and long-chain omega-3 fatty acids [24].

The efficacy of alternatives to antidepressant and benzodiazepine use during pregnancy largely depends on two changes in clinical attitude [21–23]:

1. Early detection: The obstetrician should monitor for mood disorders and adequately react to prodromal signs so that incipient disorders are treated forthwith [21,26].
2. Alternatives to medication: In pregnancy, professionally applied, evidence-based non-pharmacologic treatment for mood disorders should be preferred over psychotropic medication.

These changes may be slow to materialize in day-to-day gynecology, as they require inter-discipline cooperation. However, mood disorders, even major depression, do respond to non-pharmacologic treatment, and it is well worth our effort to try and avoid the understudied but nevertheless clearly indicated possibly negative consequences of the use of psychotropic medication during pregnancy.

5. Conclusion

The facts stare us in the face: psychotropic medication is probably harmful for the unborn. In some cases, antidepressants and anxiolytics do more harm than do depression or anxiety. The physician should aim at early detection and develop treatment strategies for both that include alternatives to medication, such as psychotherapy.

6. Condensation

Antidepressants and anxiolytics can harmfully affect the unborn child and thus are not ‘‘safe’’ during pregnancy. They should be replaced by non-pharmacologic treatments whenever possible.

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