Risk-Benefit Analysis Of Making Prescription-Only Antidepressants (OTC)

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Abstract:

This article is a dialectical discussion of the risks and benefits of making some of the currently available prescription-only antidepressants available for over the counter (OTC) use. The author performed a MEDLINE search as well as a pragma-dialectical discussion to examine the potential harm vs. benefit (or harm-reduction) of making some prescription-only antidepressants available for over the counter (OTC) use. The article also reviews the criteria that the Food and Drug Administration (FDA) uses in the re-classification of drug products from prescription to OTC (Rx-to-OTC) applications. The article concludes that there are equally convincing arguments "for" as well as "against" making some prescription-only antidepressants available in OTC forms. Despite the risks involved in making some antidepressants available for OTC use, the idea may be feasible in some parts of the world where individuals with depression may not have access to psychiatrists or the stigma is too high (such as some parts of the Arab world). The debate about risk-benefit must be local because of the uniqueness of each country's laws, rules, and regulation process as well as the uniqueness of the circumstances under which psychiatric services are rendered.

■ Introduction:

Herbal therapy, natural and dietary supplements are among many available CAM approaches to healing. The few times the term "OTC Antidepressant(s)" was used in MEDLINE was in reference to "herbal" or "natural" substances currently available OTC and used as antidepressants, such as St. John's wort, dehydroepiandrosterone (DHEA), inositol, and S-adenosylmethionine (SAMe).

■ Materials and Methods:

MEDLINE was searched for English language articles containing the terms "Over-the-Counter Antidepressant(s)" and "Over-the-Counter Psychotropic(s)." The term "Over-the-Counter Antidepressants" (pleural) occurs only once in MEDLINE, and "Over-the-Counter Antidepressant" (singular) 5 times, 4 out of the 5 studies referred to St. John's wort (or hypericin). "Over-the-Counter psychotropics" was cited in 3 articles and lumped together over-the-counter medicines like diphenhydramine and other sleep aids together with herbal, dietary supplements, or "natural" agents.

According to the Food and Drug Administration (FDA) [1] an Over-the-Counter (OTC) drug generally has the following characteristics: A) its benefits outweigh its risks, B) the potential for misuse and abuse is low, C) consumer can use it for self-diagnosed conditions, D) it can be adequately labeled, and E) health practitioners are not needed for the safe and effective use of the product. Jacobs[2] reported that, in addition to the above, the indication(s) for which the drug is to be used as OTC should be similar to its prescription indication(s), it must have favorable adverse event and drug interaction profile, low toxicity/wide therapeutic index, and no need for special monitoring.

Dialectical argumentation was found to be both useful and valid in solving conflicts in the area of health promotion.[3]

A pragma-dialectical argumentation approach[4] was used for a critical discussion of the advantages-disadvantages (or risk-benefit) analysis.

■ The potential benefits to making some antidepressants available OTC:

Empowering the patient with more autonomy in decision making: giving the patient more freedom, more choices, as well as more autonomy and responsibility to make decisions.

Overcoming stigma: In their review of four "over-the-counter psychotropics," Heiligenstein and Guenther cite "the stigma of mental illness" as partially driving college students to explore OTC psychotropics.[5] Overcoming stigma and seeing a psychiatrist for the first time may be the biggest hurdle to overcome. OTC antidepressants may reasonably help patients overcome this problem and have access to effective medicines without the stigma.

Overcoming denial: Denial and stigma are closely linked, the more the stigma the more the denial. Although there is some denial in accepting a physical illness, it is in no way close to the level of denial seen with depression and other mental illnesses.

Easier access and convenience: There is benefit in easy access to OTC antidepressants such as avoiding waiting periods for appointments and eliminating the need to travel especially in underserved areas.

More privacy and confidentiality: Concern about privacy (or the lack of it) is important in all specialties but none more than psychiatry. This is related to stigma as well. Despite all the privacy and confidentiality rules (and laws), the health care system is so complex and intertwined to the degree that there is erosion of privacy with each additional person the patient comes in contact with. It is no longer the doctor-patient relationship, it is the whole staff of the hospital, clinic, or office, as well as health insurance

companies personnel, pharmacists, secretaries, nurses, other patients, house keeping/cleaning, security, utilization review and families in the waiting area.

Cost reduction: Less cost due to saving on office visit fees and co-payments for prescriptions.

Offering patients proven and safer alternatives to what's available OTC now (herbal/natural supplement). The currently available "OTC antidepressants" are usually referred to as: Botanical Medicines, Herbal Medicine, Herbal Remedies, Dietary Supplement, and Natural Medicines among other labels. There are reported serious neuropsychiatric side effects and herb-drug interactions for herbal as well as non-herbal OTC Antidepressants[6]

- **Potential Risks:**

1. Overdose/Toxicity:

Every medication and herbal/nutritional supplement carries certain risk. Any OTC medication, herbal, natural or dietary supplement currently available has the potential of severe adverse events or even death if not taken appropriately. The Fatal Toxicity Index (FTI) is a good indicator of the lethality of a drug in clinical practice. The best current pre-clinical indicator of fatal toxicity in humans is the LD50 in animal studies. This is more important when comparing OTC toxicity to prescription drugs toxicity since FTI cannot be calculated by definition. The pre-clinical indicator of toxicity and potential lethality of the currently available OTC drugs is higher than antidepressants (using unit dose equivalents). A single dose of 10 grams acetaminophen (paracetamol) (~16 extra-strength tablets) is likely to cause liver toxicity (even death) [7] and a single dose of 23 grams acetaminophen (paracetamol) (~ 40 extra-strength tablets) is likely to be lethal. With fluoxetine (Prozac), the best data available so far is that the lethal dose in 50% of mice (LD-50) was found to be 248 mg/kg. In dogs, the minimum lethal dose is thought to be "greater than 100 mg/kg." [8] To extrapolate to humans, the lower of the two numbers means that for a 70-kg man or woman 7000 mg of fluoxetine may be the minimum lethal dose (i.e. 350 capsules of the 20mg strength of fluoxetine). This comparison makes it seem (at least preliminarily) that an OTC Prozac is safer than acetaminophen (paracetamol) as far as lethality (unit dose for unit dose, not mg for mg). Bupropion acute oral LD50 value is 482 mg/kg (female rats); by extrapolation 33,700 mg for a 70-kg human (337 tablets of the 100mg strength). For sertraline, oral LD 50 in female mice is 419 mg/kg[9] , while the minimum lethal oral dose in dogs 80 mg/kg.[6] The lower of the two figures suggests that for 70-kg human the minimum lethal dose is 5.6 grams (112 tablets of the 50mg strength). Overdose and inappropriate use can happen with almost anything, not only OTC medications, but also cleaning agents, insecticides, paint preparation and removal products, weed killers, herbal supplements, and street drugs. I believe if we disregard the individual's own responsibility, there is no end to "what might go wrong."

2. Risk of drug induced mania:

If an antidepressant is started in the depressive phase of an undiagnosed bipolar mood disorder, the risk of antidepressant-induced mania is well documented (see review of studies by Goldberg and Truman[10].

B. Is there a potential for misuse or abuse?

Risks: Poor education, irresponsibility, impatience, or thinking that higher doses mean quicker response may result in patients taking OTC antidepressants on "as needed" basis or taking higher doses than recommended. In addition, misinformed or under-informed patients may think that medication is the only answer to depression instead of considering psychotherapy as well.

Benefit: There is no indication that antidepressants are habit forming or addictive.

C. Can depression be self-diagnosed?

Risks: There is a risk of misdiagnosis especially not recognizing a bipolar depression, or depression because of an underlying medical illness.

Harm reduction: The word "diagnosis" itself is misleading in this context. Usually a diagnosis is in reference to a specific disease entity. "Depressed mood" is a self-recognized symptom and not a diagnosis. One may argue that "depressed mood" is one symptom like headache, or joint pain, whereas "Major Depressive Disorder" is a specific disease entity. It can be argued that a self-administered questionnaire or questionnaires based on the DSM criteria may allow for accurate self-diagnosis. The issue at hand is not the syndrome referred to as Major Depression but the subjective symptom "depressed mood." From a harm reduction point of view (especially applicable to underserved areas of the world) self-diagnosis and self-treatment is better than none.

D. Can some antidepressants be adequately labeled for OTC use?

The word "adequate" will no doubt create controversies: what does "adequate" precisely mean? How adequate is adequate? Who's is to judge that and by what mechanism? One may argue that adequate labeling is possible with language easily understood by lay persons. Educational labels (may be even inserts and questionnaires) may provide extra safeguards and advice. However, it may be argued that simplifying the information that should be included on a label may not be accomplished without sacrificing safety.

E. Are health professionals needed for safe and effective use?

This question needs to be qualified. Of course health professionals are needed for safe and effective use of any drug. However, this question begs clarification of "How frequent, for how long, which professional, etc. This point is insoluble from the discussion in benefit-risk analysis above. With proper education, the ability of patients to judge their own mood as well as side effects may reduce the need for health practitioners to be involved for safe and effective use of these medications. This does not need to be an all or none issue, for example OTC asthma agents or non-steroidal anti-inflammatory drugs are used following a diagnosis made by a health professional. The patient may consult a health professional (not necessarily a psychiatrist) about concerns before or after starting an OTC antidepressant.

In the USA, fear of litigation is ever-present and both litigation and fear of litigation go to extremes. The argument in favor of OTC antidepressant will be very difficult in the USA, especially with the FDA having so many pressures from different directions including the recent politico-religious pressures regarding the RU486 "morning-after pill" OTC dilemma.

- **Conclusion:**

There are risks as well as benefits to making antidepressants available OTC. The benefits include: 1) Enhanced autonomy in self-care, 2) Overcoming stigma,

3) Overcoming denial, 4) Mitigating the lack of access to services, 5) More privacy, 6) Cost reduction, and 7) Safer and effective alternatives. Risks include: 1) Self misdiagnosis, 2) Risk of inducing mania, 3) Improper use and 4) Risk of overdose/toxicity.

In the underserved parts of the world the benefits for OTC antidepressants may outweigh the risks, especially if the alternative is no treatment at all. In an ideal world, there should a complete evaluation of the patient's physical and mental health before starting an antidepressant; however, in a less than ideal world, OTC antidepressants may serve as harm-reduction options. Regulation is region-specific and this issue requires local debate taking into consideration the unique circumstances of each region of the world especially the nature of the mental health delivery system and its deficiencies.

- **References**:

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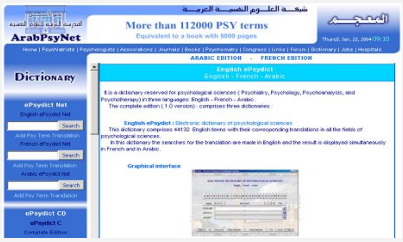

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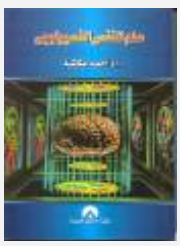

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