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Long-Term Treatment with Antidepressant Drugs: The Spectacular Achievements of Propaganda

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In the medical field, the term 'propaganda' generally refers to open and direct pharmaceutical operations (e.g. advertisements, talks by sales representatives and presents). It also has, however, a more subtle and pervasive connotation, related to media control. Noam Chomsky has been instrumental in disclosing such a link. He dates the first modern example of media control from the occasion when Woodrow Wilson was elected President of the United States in 1916, right in the middle of World War I:

'The population was extremely pacifistic and saw no reason to become involved in a European war. The Wilson administration was actually committed to war and had to do something about it. They established a government propaganda commission, called the Creel Commission, which succeeded, within six months, in turning a pacifist population into a hysterical, war-mongering population which wanted to destroy everything German, tear the German limb to limb, go to war and save the world' [1, p. 7].

Chomsky [1] analyzed the mechanisms whereby propaganda may unfold its potential: filtering information (selective perception), engineering opinion, using the public relations industry and marginalizing dissident cultures.

In his latest essay, Chomsky [2] describes how these mechanisms are operational in the world events following the September 11 tragedy (the Afghanistan war).

In the past 2 decades, clinical medicine has witnessed the emergence of special interest groups [3]. Corporate interests have fused with academic medicine to create an unhealthy alliance that works against objective reporting of clinical research (selective perception), sets up meetings and symposia with the specific purpose of selling the participants to the sponsors (engineering opinions), gets its prodigal experts into leading roles in journals, medical associations and nonprofit research organizations (public relations industry) and provides the appropriate degree of rejection of outliers (marginalization of dissident cultures).

Current trends in prescribing antidepressant drugs provide an excellent example of the risk which clinical medicine faces.

Long-Term Use of Antidepressant Drugs

The starting point of this discussion is an issue which became very apparent in the 1990s, i.e. the high rate of relapse following discontinuation of antidepressant drugs in unipolar depression [4]. On the basis of a few controlled trials, long-term use of antidepresssant drugs to avoid relapse was advocated and became a common clinical practice [5]. This led to both extension of the duration of antidepressant drug therapy to the longest possible time for treating the acute episode of depression and suggestion

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of an indefinite (lifelong) pharmacological prevention of depression. At about the same time, the effectiveness of antidepressant drugs in the short-term treatment of anxiety disorders and the chronicity of many forms of anxiety disturbances paved the way for justification of years of ongoing drug treatment [6].

The availability of antidepressant drugs which are far more tolerable than traditional tricyclics has also led to an extension of their use to forms of depression which do not reach the severity threshold of major depressive disorders and can be subsumed under the rubrics of minor depression and demoralization, despite lack of evidence for their efficacy in these situations [7]. Leading journal articles, symposia and practice guidelines push clinicians toward prescribing antidepressant drugs more and more. This propaganda, with respect to which the taint of conflict of interests has been highlighted recently in a consumer magazine [8], makes the clinician who would retain a cautious and balanced attitude feel like the person whom Chomsky [1] depicts as sitting alone in front of the TV, thinking that he must be crazy or outdated for not buying what comes out of the tube.

Selective Perception

Selective attention to the pharmacological aspects of depression therapy induced by propaganda can make the clinician unaware of a number of research findings which are worthy of clinical interest. Propaganda makes sure that these issues are neglected, if not carefully avoided. They are summarized in the following sections.

The Duration of Drug Treatment Does Not Seem to Affect Long-Term Prognosis once the Drug is Discontinued

There is evidence that casts doubt on the ability of antidepressant drugs to favorably affect the course of depressive illness, despite their recognized ability to treat the depressive episode and to prevent relapse while the patient is taking the drug. Viguera et al. [9] analyzed 27 studies with variable lengths of antidepressant treatment which reported follow-up of drug discontinuation. The duration of drug treatment did not seem to affect the long-term prognosis once the drug was discontinued. Whether you treat a depressed patient for 3 months or 3 years, it does not matter when you stop the drug (it does matter, of course, whether patients are on drugs or placebo). Indeed, there was a nonsignificant trend which suggested that the longer the drug treatment, the higher the likelihood of relapse [9]. An observational study of 236 patients with unipolar depression who had received antidepressants during recovery and were followed for an affective recurrence for up to 5 years showed that the rate of recurrence for patients with fewer than five previous episodes was not affected by medication after the initial 8 months [10].

These issues are amplified in the setting of anxiety disorders, where relapse after discontinuation of antidepressant drugs is even more common [11] and joint use of psychotherapy and antidepressants has been found to yield a worse prognosis than psychotherapy alone [12–15].

The Efficacy of Antidepressant Drugs Has Been Overemphasized

A recent analysis of 186 randomized controlled trials comparing amitriptyline with other antidepressant drugs (including selective serotonin reuptake inhibitors; SSRIs) disclosed the clear superiority of amitriptyline in terms of recovery rates [16]. Since amitriptyline is one of the oldest antidepressants, this means that while considerable progress has been made in terms of side effects profile, little (if any) has been made in terms of efficacy. Not surprisingly, the presence of residual symptomatology upon pharmacological treatment has been substantiated in the majority of successfully treated patients [4]. Residual symptoms are among the most powerful predictors of relapse [4], and their abatement by means of cognitive behavioral strategies has been found to improve long-term outcome [17–19]. The findings on residual symptoms of successfully treated depressed patients are reinforced by the very high percentage of patients who do not respond to drug treatment (up to 50%) [20]. The conclusion that can be drawn is that pharmacological treatment of depression does not provide the solution for a substantial proportion of depressive episodes and is likely to leave residual symptomatology.

Loss of Efficacy Occurs during Maintenance Treatment of Depression

The return of depressive symptoms during maintenance antidepressant treatment – which has been found to occur in 9–57% of patients in published trials [21] – is a common, vexing problem. Relapse of depression has also been found to occur during the follow-up of patients receiving tricyclic antidepressants for panic disorder [22]. Some studies point to dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug or its duration of action [23]. Other studies, however, suggest

the likelihood that pharmacodynamic processes change sensitivity to the drug [24]. In particular, the oppositional model of tolerance (continued drug treatment may recruit processes that oppose the initial acute effect of a drug or its receptor modifications) seems to entail a considerable explanatory power [23, 25]. In clinical terms, increasing the dosage of the antidepressant drug does not always help, and, when it does, it may yield only temporary relief. Since this is a very touchy area for the pharmaceutical industry, there is insufficient research on these crucial clinical issues.

The Full Meaning of Withdrawal Reactions from Antidepressant Drugs Is Not Appreciated

Withdrawal symptoms following discontinuation of antidepressants were recognized soon after the introduction of these drugs [26]. They have been described with all types of antidepressant drugs, but particularly with SSRIs [27–30]. From a randomized controlled trial [31], we know that not all SSRIs induce a 'discontinuation' syndrome (as the propaganda of special interest groups redefined withdrawal reactions) to the same degree; fluoxetine is less prone to do so than paroxetine or sertraline. What we do not know is what all this really means. Are withdrawal phenomena simply bothersome and self-limiting reactions or are they a sign of something else? As Grahame-Smith [32] has aptly stated: 'Chronic drug therapy may induce a sleeping tiger, which awakens when the drug therapy is stopped and results in rebound withdrawal effects with serious consequences, as with many drug addictions' [p. 227]. But what is this 'sleeping tiger'? The inverse relationship between the duration of maintenance antidepressant treatment and the time to recurrence off treatment [9] raises concern about the induction of a vicious circle. It in fact suggests the possibility of an addiction model whose most immediate clinical manifestations are withdrawal symptoms [29]. According to a sensitization hypothesis [23], antidepressant drugs may facilitate relapse once they are discontinued and worsen illness outcome. The possibility that antidepressant drugs may induce acceleration of episodes has not been adequately studied in unipolar depression, but it is widely recognized in bipolar disorder [23]. Goodwin [33] has illustrated how this could occur. If both depressive and manic episodes tend naturally to evolve toward remission (either into a euthymic phase or into an episode of opposite polarity), and if antidepressant drugs accelerate this natural tendency, drug treatment may accelerate the next sequence in the natural course (i.e. the onset of a manic episode instead of euthymia). Goodwin [33] stated it thus: 'If the natural sequence of recurrent unipolar illness goes from depression to recovery and then eventually to the next episode, treatments that accelerate recovery of the index depression could also accelerate the onset of the next episode' [p. 43].

These clinical phenomena (withdrawal and sensitization) may also apply to the long-term use of antidepressant drugs in anxiety disorders [11, 34].

Nonpharmacological Prevention Strategies Are Neglected

It is ironic that while psychiatrists view prevention of relapse of depression purely in pharmacological terms as if it were a disease such as diabetes [5], diabetologists emphasize the importance of nonpharmacological strategies (lifestyle modification) in the prevention of type 2 diabetes mellitus [35]. This is a perfect exemplification of a phenomenon described by Lipowski [36] in the late 1980s: '... after a period marked by one-sided emphasis on psychodynamics and social issues, or what could be called "brainless" psychiatry on account of its relative neglect of cerebral processes, we are witnessing an opposite trend towards extreme biologism or "mindless" psychiatry' [p. 244].

Yet, there is now extensive evidence for the role of cognitive behavioral psychotherapy in the prevention of relapse in unipolar depression [17–19, 37–40].

Ryff and Singer [41] remark that mental health research is dramatically weighted on the side of psychological dysfunction and that health is equated to the absence of illness rather than to the presence of wellness. They suggest that the absence of well-being creates conditions of vulnerability to possible future adversities and that the route to recovery does not lie exclusively in alleviating the negative, but also in engendering the positive. In depression research, little attention is paid to the balance between positive and negative affects [42] and to the promotion of psychological well-being [17]. Similarly, lifestyle modification, which is widely practiced for the prevention of relapse in myocardial infarction [43], is not even considered in clinical psychiatry, despite the fact that depressed patients are often unaware of the long-term consequences of a maladaptive lifestyle which does not take chronic stress, interpersonal friction and excessive and inadequate rest into consideration [17].

Is This the Right Way?

Antidepressant drugs were developed and found to be effective in the treatment of the major depressive episode [44]. In recent years, however, their use has been prolonged and extended to maintenance and prevention, with apparently reassuring results in comparison with placebo [45]. However, treatments that are effective in the acute phase of illness are not necessarily the most suitable for postacute and residual phases or maintenance [46].

If we are able to remove the conceptual obstacles that obstruct our view [47] and silence the sound of propaganda, we may then become aware of a different scenario.

We are stretching the original indications (major depressive episodes) of drugs of modest efficacy to include prevention of relapse, anxiety disorders and demoralization. Patients do not suddenly become well, but tend to gradually lose their depressive symptoms over the months following treatment [48]. Stassen et al. [49] found that the time course of improvement among responders to amitriptyline, oxaprotiline and placebo was independent of the treatment modality and thus identical in the three groups. Once triggered, the time course of recovery from illness became identical to the spontaneous remission under placebo. Antidepressant drugs, therefore, may not change the pattern of the natural course of recovery from depressive illness, but simply speed the recovery and change the boundary between 'responders' and 'nonresponders' [49]. When we prolong treatment over 6–9 months, we may thus recruit different phenomena, such as tolerance, episode acceleration, sensitization and paradoxical effects [23]. Antidepressant drugs may still be superior to placebo, but their hidden costs may far outweigh their apparent gains.

A series of excellent studies by a research group in Seattle is illustrative of this unfair trade. Three hundred and eighty-six patients with recurrent major depression or dysthymia who had recovered after 8 weeks of antidepressant treatment prescribed by their primary care physicians were randomized to a relapse prevention program (based on pharmacological treatment) or standard primary care [50]. There were no significant differences in episodes of relapse. However, patients in the intervention group were significantly more likely to refill medication prescriptions over the 12-month follow-up. In another study [51], there were no substantial differences between depressive patients treated by psychiatrists and those treated by primary care physicians. A third investigation [52] disclosed significant differences between an intervention arm (based on the use of paroxetine) and a standard-care arm in panic disorder, particularly in the first 6 months. We wonder, however, what would happen subsequently, if patients tried to discontinue paroxetine. Even if they were treated with an approach entailing enduring effects (cognitive behavioral therapy), their course would be less favorable than if paroxetine had not been used at all [12–15].

Carroll [53] anticipated the effects of inappropriate trends in the prescribing of antidepressant drugs 2 decades ago, in the following statement: '... we strongly suspect that many patients who are simply unhappy or dysphoric receive these drugs, with predictable consequences in terms of mortality from overdose, economic waste and irrational, unproductive clinical management'.

Table 1. Steps for implementing the sequential approach in recurrent depression [56]

1.	Careful assessment of the patient 3 months after antidepressant drug treatment, with both observer-rated instruments (with special reference to anxiety and irritability) and self-observation (diary)
2	Cognitive behavioral treatment of residual symptoms (cognitive restructuring and/or homework exposure), if present
3	Tapering of antidepressant drug treatment at the slowest possible pace (such as 25 mg of a tricyclic every other week)
4	Well-being-enhancing therapy (well-being therapy) and lifestyle modification
5	Discontinuation of antidepressant drugs
6	Careful assessment of the patient 1 month after drug discontinuation

An Alternative Approach

In recent years, a new way of integrating pharmacotherapy and psychotherapy in depression has been proposed, i.e. the sequential approach [54]. According to this model, which has been validated in randomized controlled trials in unipolar depression [17–19, 38] and in a pilot investigation in bipolar disorder [55], pharmacotherapy is used in the acute phase of depression and cognitive behavioral psychotherapy in the residual phase. Its preventive effects appeared to be related to the abatement of residual symptoms and/or an increase in psychological well-being and coping skills.

The practical steps for implementing this approach are described in table 1 and detailed elsewhere [56]. It may include discontinuation of antidepressant drug treatment, as outlined here, or its maintenance. It may offer the

advantage of yielding enduring effects while limiting the exposure to drug therapy.

As to anxiety disorders, effective cognitive behavioral strategies have been developed which are likely to entail long-lasting effects [11–15]. These therapies challenge the routine use of antidepressant drugs, unless specific clinical situations occur, such as depression comorbidity.

Not surprisingly, advocates of nonpharmacological treatment strategies are swimming against the tide of pharmaceutical propaganda. Those who are involved in mental health (both as care providers and consumers), however, should be aware that life after antidepressant drugs does exist and that it may be far more gratifying for both. Psychiatrists, in particular, may rediscover the spectacular achievements of competent treatment and the joy of intellectual freedom.

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