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The Work of Antidepressants: Preliminary Notes on How to Build an Alliance Between Feminism and Psychopharmacology

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Abstract
Most feminist analyses of pharmaceutical medication engage with social or cultural concerns. This commentary will be more organic in focus. Is it possible that biological treatments of depression are more politically interesting than hitherto imagined in feminist scholarship? I will argue that innovative analyses of the body and psychological distress are possible when one is closely attuned to the detail of psychopharmaceutical treatment.

Keywords Antidepressants, Brain, Embodiment, Feminism, Gut, Neurology

Can feminism work with antidepressants?

I am not asking whether or not feminists should advocate the use of antidepressant medications. Rather I am interested in how feminism might become more engaged with the data and models that have emerged from the recent expansion in pharmaceutical treatments of depression. Are there aspects of the post-Prozac landscape—especially new biological data—that feminism could use to expand and invigorate its activities? To put this simply: what might feminism learn from the psychopharmacology of depression?

One of the central difficulties in generating a useful dialogue between feminism and psychopharmacology is the anti-biologism of contemporary feminist theory. It has become axiomatic that culture rather than nature is the proper sphere for feminist politics. This presumption underpinned the success of social constructionism as the premier mode of feminist analysis in the social sciences in the 1990s. Indeed, the turn against biological explanation was so conceptually lucrative for feminism that it now seems a nonsense to think of biology as a site of transformation or innovation (Wilson, 2004b). This schism between politics and biology remains a significant obstacle for feminist work in the current psychocultural climate. Without conceptual interest in how biology invents, transforms, crafts, redistributes,

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incorporates and bequeaths, feminists will remain perplexed by the character of psychopharmaceutical events.

In this commentary, I offer a preliminary analysis of how feminism and psychopharmacology could be brought into a more dynamic and fruitful alliance. I will argue that close attention to pharmacological data opens up new avenues for analysing the embodiment of melancholy.

Pharmacokinetics

Let me begin with a prosaic but important datum about the new antidepressant medications: they are all administered orally.[1] That is, they are manufactured in tablet form, and they are swallowed. While it is the case that most pharmaceuticals are administered orally, there is particular significance in the oral administration of antidepressants: there is an intimate connection between the gut and depression, making intervention via the gut an especially felicitous means of treatment for depressed mood (Wilson, 2004a). While conventional neuroscientific and psychiatric texts often posit a direct link from drug to brain, close attention to the details of drug absorption, distribution, metabolism and excretion (what is called the drug's pharmacokinetics) shows that the viscera are also essential to how disorders of mood become instantiated and how they can be treated. Rather than validating a single, central site of determination for mood (the brain), the pharmacokinetics of antidepressant drugs shed light on how depression is distributed, in both organic and psychic registers, all through the body.

What are the pharmacokinetic trajectories of an antidepressant? For any orally administered drug, the gastrointestinal (GI) tract is the site at which the drug is absorbed into the body, and GI distress (nausea, delayed gastric emptying and constipation) is a commonly experienced adverse effect. Because oral administration of drugs is so widespread, management of the gut's response to drugs has become a crucial part of pharmaceutical research. For example, there are numerous technologies available for controlling where in the GI tract drugs are released. Tablets can be specially coated so that they don't dissolve in the stomach but will dissolve in the intestine; or pills can be manufactured to float on the gastric juices, thus extending their time in the stomach (Jantzen and Robinson, 2001). In most cases, the gut itself is not the target of therapeutic action; the drug is being released into the body some distance from its intended site of action (Katzung, 2001). The pathways from the gut to that target site are often circuitous, and it is these pathways that have arrested my critical interest.

1 The new generation antidepressants include the selective serotonin reuptake inhibitors (SSRIs) Prozac/fluoxetine, Zoloft/sertraline, Paxil/paroxetine, Celexa/citalopram, and Luvox/fluvoxamine. As well as the SSRIs there are new 'atypical' antidepressants that came onto the US market around the same time: Serzone/nefazodone, Effexor/venlafaxine and Wellbutrin/bupropion. These drugs are more heterogeneous in their pharmacological action—they are less specific to the serotonin system and act on other neurotransmitter systems, specifically norepinephrine (Potter and Hollister, 2001). They are sometimes called third generation, heterocyclic or serotonin-norepinephrine reuptake inhibitors (SNRI) antidepressants. Prozac/fluoxetine is manufactured in liquid and oral form. The other SSRIs and the other atypical antidepressants are only manufactured in oral form (Potter and Hollister, 2001). Some of the well-established tricyclic antidepressants (e.g. Elavil/amitriptyline and Tofranil/imipramine) can be administered by injection: 'Intramuscular administration of some tricyclic antidepressants (notably amitriptyline and clomipramine [Anafranil]) can be performed under special circumstances, particularly with severely depressed, anorexic patients who may refuse oral medication or ECT' (Baldessarini, 2001: 463).

A drug like an antidepressant that is intended for the central nervous system (CNS) must first pass from the gut lumen into the bloodstream. Once it has passed though the gut mucosa, the drug is transported via the portal vein to the liver where enzymes remove a certain amount of the drug (this is called first-pass clearance). From the liver, the remaining percentage of the drug moves into general (systemic) circulation in the body, where it is distributed into the fluid inside and between the cells of the body's tissues and organs. The brain is targeted rapidly, as are the liver, kidneys and other organs that are well supplied with blood. Eventually (this can take anywhere from several minutes to several hours) muscle tissue, the remaining viscera, the skin and the body's fat will also be infused with the drug (Wilkinson, 2001).[2] The first thing to note, then, is that the physiological itinerary of an antidepressant takes in every organ of the body. Might we not wonder about antidepressant effects of drug action at these other sites?

The passage of a drug from systemic circulation into the brain is also quite intricate. The brain is protected by a barrier that prevents the transit of large molecules and potentially toxic solutes from the blood into the brain itself (Begley, 2003). Serotonin, for example, cannot pass the blood–brain barrier (it is too large). Even though there are significant reservoirs of serotonin in the rest of the body,[3] the brain must synthesize its own serotonin from other, smaller molecules that are able to cross the blood–brain barrier. To put this in quotidian form: it isn't possible to increase serotonin levels in the brain simply by ingesting more serotonin. One of the ways in which the blood–brain barrier functions is simply obstructive—the cells that make up the walls of the brain's capillaries are so tightly packed together that drugs are not able to pass between these cells into brain tissue, as they would in other parts of the body (Begley, 2003). Prevented from passing *between* cells, drugs must pass *through* the cells, and to do this they require some assistance from a chemical transport system. One of the most widely used methods for getting drugs across the blood-brain barrier is to make them lipid-soluble—the more lipophilic a drug is, the more readily it will cross the blood-brain barrier (Wilkinson, 2001). SSRIs are small molecules that are lipophilic, and they readily pass across the blood–brain barrier (Brøsen and Rasmussen, 1996).

Once inside the brain, SSRIs (selective serotonin reuptake inhibitors) are thought to increase the amount of serotonin that is available for neurotransmission (by inhibiting its reuptake in the synapse); and in turn this increase in serotonin is thought to elevate mood. It has been conventional (in both biopsychiatric texts and the political literatures that agitate against them) to focus on this particular destination of an antidepressant—as though the cerebral synapse were an antidepressant's natural or most important coalface. My interest has been diverted elsewhere—to the many biological sites and processes

2 Each of the SSRI antidepressants varies in terms of how much of the drug reaches systemic circulation. This is called a drug's bioavailability. The bioavailability of Paxil/paroxetine is around 50%, for example. Prozac/fluoxetine has a reasonably high bioavailability (70%) and Luvox/fluvoxamine is even higher (greater than 90%) (Potter and Hollister, 2001). The differences in bioavailability are further amplified by the fact that the metabolites of the SSRIs (i.e. the substances produced by metabolism of the drug in the liver and elsewhere) can also have antidepressant effects. The metabolite of fluoxetine (norfluoxetine), for example, is four times more potent as a serotonin reuptake inhibitor than is fluoxetine itself.

3 Ninety-five percent of the body's serotonin is stored outside the CNS—in the blood and in the extensive network of nerves that encases the gut (Wilson, 2004b). In fact, serotonin was first discovered in the blood, where it was understood to be a vasoconstrictor (thus the name sero-tonin: a serum agent affecting vascular tone). It was some years before it was located in the brain and accepted as a neurotransmitting substance, in both the central and peripheral systems (Gershon, 1998).

implicated in the ingestion of an antidepressant pill. It seems to me that too narrow a focus on the brain occludes other important events in antidepressant metabolism, making it difficult to think anew about the nature of body-mind relations.[4]

Body and brain

There are two issues I would like to draw out of these data that may help inform feminist theories of body and mind.

First, drugs work with the whole body. While antidepressants may be intended for the brain, their therapeutic effects are gleaned from a wide variety of responses in other organs. Given that SSRIs and SNRIs (serotonin-norephinephrine reuptake inhibitors) are widely distributed in the body by systemic circulation and that they work effectively on synapses in the CNS, it would seem likely that they are also targeting the synapses of the nerves in the peripheral nervous system, especially the gut. Any pharmaceutical alleviation of dysthymic symptomatology, then, cannot be attributed solely to effects in cortical and subcortical structures in the brain, it must also include the soothing and animating effects on the viscera (Wilson, 2004a, 2004b). Pharmacokinetic data support models of the body in which simple lines of cause and effect (drug to brain to mood) are refracted; and these data are immensely valuable for feminism, as it argues for more dynamic and expansive accounts of the body. Close observation of these data finds not biological determinism but biological overdeterminism.[5]

Even though the viscera are not mentioned as target sites for SSRI action in psychiatric or pharmacological texts, the effective pharmaceutical treatment of depression requires engagement with the organic periphery as well as the brain. Perhaps because the gut is the delivery system for these drugs, it has been thought of as simply a conduit for drug action and not as a participant in the drug's therapeutic effects. Conceptual schemata that privilege the centre over the periphery, or that draw radical distinctions between (active) agents and (passive) vessels have been the target of ongoing feminist intervention (e.g., Keller, 1995). If the neurological and pharmacological sciences have been particularly forceful sites for reinforcing these problematic conceptual structures, it seems to be despite the data they are generating, not because of them. Indeed, the neurological and pharmacokinetic data on antidepressants strongly indicate that the body as a whole is implicated in depressive states. The

4 For critics like Peter Breggin (Breggin and Breggin, 1994) this distribution of antidepressant effect beyond narrowly defined serotonergic pathways in the brain is one of the signs that drugs like Prozac are toxic substances. Breggin's work is politically ineffectual, in my view, because it doesn't use this dissemination of drug effect to rethink conventional models of biological substrate and psychological malady. After all, the allegedly toxic effects of antidepressants are no less illuminating than their supposedly therapeutic effects. Does this data not provoke conjecture about the nature of sexual function or sleeping patterns or suicidal intent such that they may be rerouted by a molecule? If it is simply facile to say that psychology is fabricated beyond the reaches of biochemistry, or that psychology is entirely prescribed by biochemistry, then what models of biopsychic imbrication might we start to imagine? To the extent that Breggin accepts a very conventional model of direct and unwavering lines of influence from drug to body to mind ('Prozac made me kill my wife'), he is more faithful to mainstream biopsychiatry than he suspects.

5 Here I am leaning on the Freudian notion of psychic overdetermination (Überbestimmt). Freud suggests that in hysteria the psychic determinants of a symptom follow 'an irregular and twisting path' (Freud and Breuer, 1895: 289). These paths form complex networks of determination: 'the logical chain [of meaning] corresponds not only to a zig-zag, twisted line, but rather to ramifying system of lines and more particularly to a converging one' (1895: 290). I am attempting to excavate similar webs of overdetermination in pharmacological systems.

viscera aren't mere transfer stations for agents that will have their effects elsewhere. Rather, the liver and the gut provide the bioaffective tone of depressions: if your depressions are agitated, or soporific, or angry, or anorectic that is due in no small part to the attitude of the visceral organs. It appears that the co-assembly of these traits with cognitive and ideational schemata (suicidality, hopelessness, guilt) is what generates a depressive condition serious enough to warrant intervention and treatment.[6]

The second issue I would like to consider in the pharmacokinetic data concerns the brain and its interface with extra-cerebral systems. Just how isolated and autocratic is the brain? Are the biological bases of dysthymic states exclusively cerebral? Neurological and pharmacological descriptions of the blood-brain barrier often stress the sequestration of the brain: 'a major function of the [blood-brain barrier] is that of neuroprotection. Over a lifetime the CNS will be exposed to a wide range of neurotoxic metabolites and acquired xenobiotics, which may cause cell damage and death' (Begley, 2003: 84). Notions of the brain as an autonomous, self-contained organ are common enough in both the scientific and popular imaginary. However, the pharmacological work on the blood-brain barrier seems less interested in the defensive and segregating nature of the barrier, than in its function as a system of transportation and communication with the outside. As we follow these data, we find that the brain is always, necessarily implicated in relations with other organs and other extra-bodily systems; the blood-brain barrier is one particularly intensive site for such xenobiotic transmissions.

For example, the brain doesn't manufacture serotonin internally and independently of the body. Rather, the synthesis of serotonin requires ongoing commerce between the brain and the gut and the cultural milieu. The basic building block of serotonin is tryptophan, an amino acid that is small enough to cross the blood-brain barrier. Tryptophan is an essential amino acid, which means it cannot be manufactured by the body—it must be supplied to the body as part of the diet. Chocolate, bananas, milk, meat and fish are all high in tryptophan. The production of CNS serotonin is further complicated by the amount of carbohydrate that is ingested in the diet. If the diet is heavy in carbohydrates (bread, cake, ice-cream), the body will produce insulin in order to control high blood sugar. The insulin will remove most of the other amino acids from the blood, reducing competition at the blood-brain barrier, and allowing a disproportionate amount of tryptophan to pass from the blood to the brain (Wurtman *et al.*, 2003). This means that levels of serotonin in the brain are dependent on a number of extra-cerebral systems: for example, enzymes in the liver, conditions in the gut lumen, and the psychocultural milieu governing diet. No one of these systems entirely governs serotonin traffic. Rather, serotonergic activity is an overdetermined network of relations among organs, and among biological and cultural and psychological systems.

6 The contemporary psychoanalytic clinical literature now emphasizes the complex overdetermination of psychopathology. It is the confluence of attachment patterns, neurobiological inclinations, affect scripts, unconscious motivations and cognitive schemata that generate psychological symptoms. The work of Allen Schore (2003), for example, has been particularly influential in bringing neurobiology to bear on contemporary psychotherapeutic practice in innovative ways. Schore focuses almost exclusively on the CNS when thinking about the neurobiology of self states (and he is less interested in depressive conditions than in the sequelae of trauma on the development of personality). Here, I am trying to think in tune with authors like Schore, but in a more visceral register.

Any regulation of the serotonergic system—including the ingestion of SSRIs to regulate mood—must grasp this network logic in order to be successful. A narrow focus on the brain as the sole biological source of psychological malady will obstruct the lines of connection that tie organ to organ, and that underpin the biological possibility of recovery. To paraphrase Winnicott (1964)—there is no such thing as a brain, there is always a brain and another system.[7] My hypothesis is this: the biological disintegration of mood is a breakdown not of the brain *per se*, or of the liver or the gut—it is a breakdown of the relations among organs. The pharmaceutical treatment of depression has to be the management—not of a place or a centre or even a neurological pathway—but of an organic capacity to connect.[8] When they work, SSRIs reiterate the serotonergic networks that traverse the body and reanimate the natural affinities among organs. Effectively administered, SSRIs can promote a profound, long-lasting, organic empathy.

Biological politics

Of course, feminists have argued that psychopharmaceuticals are often not effectively administered. There is also extensive debate in the feminist and affiliated literatures about whether antidepressants, in particular, work in the manner promoted by pharmaceutical manufacturers (e.g. Healy, 2004). These critics tend to emphasize the social motivations for keeping women medicated; they are critical of the practices of pharmaceutical companies and the doctors who collude with them, and they remain dubious about the efficacy of pharmaceutical treatments for conditions they diagnose as essentially cultural in origin (e.g. Griggers, 1997; Zita, 1998). In this short commentary, I have taken a different approach to the nexus of feminism and psychopharmaceuticals—one that is more directly engaged with the biological substrata of psychological disequilibrium. This orientation is governed by my conviction that effective political engagement with the contemporary life sciences requires ongoing intimacy with their data. It is my expectation that close, conceptually rigorous attention to biological detail will procure more dynamic models of depression than we have hitherto suspected.

7 'I once risked the remark, "There is no such thing as a baby"—meaning that if you set out to describe a baby, you will find you are describing *a baby and someone*. A baby cannot exist alone, but is essentially part of a relationship' (Winnicott, 1964: 88).

8 This is argued in more depth in Wilson (2004b: 43ff).

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