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A Basic Drug Formulation Appropriate for Many Psychiatric Diagnoses

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Abstract- This article proposes a basic drug formulation that, with additions according to the particular behavior, addresses all psychiatric conditions. The drugs examined are those that address the five major types of brain cells, neurons, astrocytes, oligodendrocytes, endothelial cells and microglia. Approximately 40 drugs need consideration. Five of those drugs have the widest activity but drug-drug interactions eliminate fluoxetine, leaving ketamine, metformin, minocycline, and valproate, as the drugs for formulating a basic treatment for all psychiatric conditions.

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A Basic Drug Formulation Appropriate for Many Psychiatric Diagnoses

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I. Background

Is there a basic formulation of drugs that, with additions according to the particular behavior, is appropriate for all psychiatric diagnoses? Behavior, whether involving cognition, emotion, decision-making, or voluntary movement, is brain-based; possible exceptions are reflexive or autonomic. Thus, abnormal behavior, i.e., psychological or psychiatric disturbance, is normally also brain-based even when the immediate, apparent causes were environmental or societal. Because the molecular biology of brain function depends upon some of the five major types of brain cell, i.e., neurons, myelinating oligodendrocytes, astrocytes, endothelial cells, and microglia, changing any brain function requires addressing one or more of those brain cells. The biochemical events in those cells during abnormal behavior, might not be seen directly but may be discerned indirectly by finding the drug or drugs that benefit a particular function and noting the mechanisms that are known to derive from such drugs. Thus, if condition 'a' is benefitted by drug 'b', and drug 'b' benefits mechanisms 'c, d,...n', the mechanism by which drug 'b' benefits condition 'a' might be contained in 'c,d,...n'. Pragmatically, if a psychiatric condition is reliably benefitted by one or several drugs, the mechanism that is responsible for that benefit may be ascertained from the known effects of those particular drugs. If the same drugs were useful for treating several psychiatric conditions, then using those drugs plus others appropriate for the particular condition being treated, should be a basic formulation that benefits all such conditions.

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II. Introduction

If all psychological and psychiatric abnormalities have a biological basis, then it is possible that they may all be addressed by a basic drug formulation that would, necessarily, derive from addressing the changed function of the brain cells that underpin all brain functions. The following discussion shows how the functions of each of the five types of brain cell may be influenced by available drugs, so that a formulation of drugs for a basic treatment regimen might be applicable.

1. *Neuronal Cell Function:* A huge number of drugs enhance neuronal function, doing so by acting on neurotransmitters, ion channels, receptors, metabolism, or other intracellular signaling pathways.

Multiple drugs promote neurotransmission, including L-dopa and dopamine agonists (e.g., pramipexol and ropinirole) via the dopamine receptor 3[1], monoamine oxidase inhibitors that reduce breakdown of dopamine (e.g., selegiline and rasagiline)[2], cholinergic drugs (acetylcholinesterase inhibitors e.g., donepezil, rivastigmine)[3]; glutamatergic drugs that either block NMDA receptors (e.g., memantine or ketamine)[4] or enhance AMPA/NMDA, GABAergic drugs (benzodiazepines that increase the frequency of Cl^- channel opening, barbiturates that increase the duration of Cl^- channel opening[5]; valproate that inhibits GABA transaminase)[6], Na^+ channel blockers (e.g., phenytoin)[7]; Ca^{++} channel blockers (e.g., gabapentin)[8], neurotrophic agents (e.g., the SSRI fluoxetine), neuroprotective agents (e.g., GLP-1 agonists such as liraglutide, thiamine needed for glucose metabolism in neurons, mitochondrial function enhancement (coenzyme Q10 and nicotinamide riboside), anti-inflammatory/microglia-modulating (e.g., minocycline that inhibits microglial activation), increase of dopamine/norepinephrine by using methylphenidate or amphetamine to support neuronal growth and survival, and IGF-1 and insulin to modulate social and emotional processing.

2. *Astrocyte Function:* Is both neuroprotective and anti-inflammatory. It is influenced by a variety of drugs. Minocycline reduces activation by astrocytes of microglia and decreases pro-inflammatory cytokine release[9]. Ibudilast (approved in Japan but not yet in the US) inhibits phosphodiesterases and

macrophage migration inhibitory factor (MIF), reduces astrocyte-mediated inflammation[10]. Low to mid-range levels of glucocorticoids suppressed inflammatory gene expression (e.g., *IL-6, TNF-α)*[11] in astrocytes. Ceftriaxone increased expression of glutamate transporter EAAT2 (GLT-1) and alters glutamate uptake in astrocytes[12]. Valproic acid also influences astrocytic glutamate metabolism, as well as anti-inflammatory signaling and histone deacetylase inhibition, and also alters astrocyte gene expression[13]. Treatment with metformin maintained a significantly higher number of oligodendrocytes and its precursor cells, improved myelination and lowered activated astrocytes and microglia[14]. Thiamine supports astrocyte energy metabolism; its deficiency causes astrocyte dysfunction and Wernicke's encephalopathy[15]. Fluoxetine (SSRI) increases secretion of BDNF from astrocytes, and modulates gliotransmission[16]. Ketamine stimulates multiple pathways including astrocytic glutamate and inflammation, and promotes neuroplasticity[17], and influences calcium signaling and the anti-inflammatory pathway in astrocytes[17].

3. *Oligodendrocyte Function:* Clemastine promotes differentiation of oligodendrocytre precursor cells (OPC) and therefore enhanced remyelination in both multiple sclerosis (MS) models and a clinical trial for MS[18]. Benztropine promotes differentiation of OPC[19], and so does metformin, via activation of AMPK[14,20]; so both drugs promote remyelination. Remyelination did not adequately occur in the absence of IGF signaling, and OPCs did not proliferate or survive as well without IGF1; thus, IGF-1 promotes oligodendrocyte survival and, therefore, myelination [21].
4. *Endothelial Function:* Statins upregulate nitric oxide synthase (NOS) and thus increase nitric oxide (NO) bioavailability; they also reduce reactive oxidative stress (ROS), inflammation, and low density lipoprotein (LDL) oxidation[22]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) e.g., enalapril and losartan, promote improved endothelial-dependent vasodilation via reduced angiotensin II-induced oxidative stress and inflammation[23]?. GLP-1 receptor agonists (e.g., liraglutide, semaglutide) reduce endothelial inflammation and reactive oxygen species (ROS) via activating GLP-1R in endothelial cells, causing promotion of anti-inflammatory signaling[24]. Metformin improves endothelial NO production and reduces reactive oxidative stress (ROS) via activating AMPK, and enhancing NOS activity and mitochondrial function[25]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors e.g., empagliflozin, dapagliflozin, reduce endothelial dysfunction[26], reduce oxidative stress, and improve mitochondrial function[27]. Thiazolidinediones e.g., pioglitazone improved insulin sensitivity via activation of PPARγ, and reduced inflammation[28]. Omega-3 fatty acids improve endothelial cell-induced vasodilation, and reduce inflammation[29].
5. *Microglial Function:* May be changed either by modulating its activation to being pro-inflammatory versus anti-inflammatory, altering its phagocytic activity, or influencing its production of cytokines (see above). Minocycline reduced formation of pro-inflammatory cytokines (IL-1β, TNF-α), and decreased ROS[30]. Ibuprofen and other NSAIDs inhibited COX enzymes and thus suppressed microglial-mediated inflammation[31].. Signaling by glucocorticoid receptors down-regulated microglial inflammatory gene expression[32]. Drugs such as pioglitazone (a PPAR-γ agonist) or rosiglitazone, promote alternative activation of microglia by switching their morphology from M1 (pro-inflammatory) to M2 (anti-inflammatory)[33]; they may also reduce deleterious production by microglia of NO and TNF-α[34]. Rapamycin (mTOR inhibitor) inhibits microglial proliferation, so reduces their activation and expression of inflammatory cytokines[35].

Choice from Multiple Drugs

Over three dozen drugs are listed in the above paragraphs. Rational choice of a regimen should be based upon those drugs with the widest therapeutic effects. In the above list, those include fluoxetine, ketamine, metformin, minocycline, and valproate;. Using only those five provides a more manageable number. Ketamine blocks NMDA receptors[17] and valproate is a GABAergic drug[13], so both agents have wide effects; fluoxetine increases secretion of BDNF from astrocytes, and modulates gliotransmission[16]; metformin enhances endothelial nitric oxide (NO) activity and so improves endothelial NO production; it also reduces reactive oxidative stress (ROS) via activating AMPK, and enhances mitochondrial function[25]; minocycline inhibits microglial activation, reduces pro-inflammatory cytokines (IL-1β, TNF-α), and decreases ROS[30].

Drug-drug interactions cannot be ignored in creating a drug formulation. Fluoxetine + valproate may increase valproate levels, raising the risk of CNS depression, hepatic toxicity, or thrombocytopenia, so these two should not be co-administered. Fluoxetine may increase the hypoglycemic effect of metformin, so blood glucose levels must be monitored, especially at initiation or dose change. Fluoxetine + ketamine risks causing the serotonin syndrome since both have serotonergic effects, so these two drugs should not be administered together. For these reasons, it would be prudent to remove fluoxetine from the final drug

formulation. Valproate + minocycline may rarely increase intracranial pressure, which may be monitored by observing for vision changes and headache.

Provisionally, then, using four drugs, ketamine, metformin, minocycline, and valproate, would allow formulation of a basic treatment regimen for all psychiatric abnormalities with additions depending upon the specific abnormality being treated.

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