REVIEW

Allostatic Load as a Tool for Monitoring Physiological Dysregulations and Comorbidities in Patients with Severe Mental Illnesses

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Severe mental illnesses like schizophrenia and bipolar disorder are disabling, chronic conditions that are often accompanied by medical comorbidities. In this theoretical article, we review the allostatic load model representing the "wear and tear" that chronic stress exacts on the brain and body. We propose an innovative way of monitoring physical and psychiatric comorbidities by integrating the allostatic load model into clinical practice. By interpreting peripheral biomarkers differently, medical professionals can calculate a simple, count-based, allostatic load index known to predict diverse stress-related pathologies. In addition to screening for comorbidities, allostatic load indices can be used to monitor the effects of pharmacological and psychosocial interventions. This framework can also be used to generate a dialogue between patient and practitioner to promote preventive and proactive approaches to health care.

Keywords: allostatic load, bipolar disorder, chronic stress, comorbidities, pharmacological allostatic load, schizophrenia, severe mental illness

The lifetime prevalence for both schizophrenia and bipolar disorder is estimated to be 0.4% worldwide.[1] As listed in Tables 1 and 2, medicated schizophrenia and bipolar disorder patients have an elevated risk of comorbidity and elevated mortality rates. For psychiatrists, these statistics present the compounded challenges of monitoring patients' responses to pharmacological and psychosocial treatment as well as the development of comorbidities such as substance abuse, diabetes, cardiovascular disease, and obesity. This endeavor could be facilitated, and clinical outcomes improved, by refining screening technologies to better predict comorbidities, thereby enabling clinicians to intervene proactively rather than reactively. We propose that the allostatic load (AL) model—which represents a multisystemic and subclinical approach to measuring physiological dysregulations—represents an innovative approach to preventing comorbidities among patients with schizophrenia or bipolar disorder.

Allostatic load refers, in effect, to the "wear and tear" that chronic stress exacts on the brain and body. AL indices[5] incorporate several dysregulated biomarkers associated with numerous health outcomes (for reviews, see Beckie [2012][6] and Juster et al. [2010][7]) that are markedly more prevalent among patients with schizophrenia and bipolar disorder. The AL model has not yet been empirically or clinically applied to this population, however, though Kapczinski and colleagues[8] have published an excellent synthesis of the interconnections between AL and bipolar disorder. And since chronic psychosocial stress is pathogenic and pervasive in schizophrenia and bipolar disorder, it follows that monitoring the physiological recalibrations associated with AL could inform research and practice.

This theoretical review article uses synthesized literature gathered using PubMed, Web of Science, and PsycInfo engines, along with the Papers software developed by Mekentosj. Our goal is to apply the AL model to schizophrenia and bipolar disorder in order to monitor physiological dysregulations and comorbidities. While we focus on schizophrenia and bipolar disorder as *severe mental illnesses* (SMI), the

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Table 1
Prevalence of Comorbidities Among Medicated Schizophrenic and Bipolar Patients

Condition	Comorbidity	Estimated prevalence of comorbitiy (as percentages)	Relative risk compared to general population
Schizophrenia	Obesity	45–55	1.5–2
	Diabetes	10–15	2
	Hypertension	19–58	2–3
	Dyslipidemia	25–69	≤5
	Metabolic syndrome	37–63	2–3
Bipolar disorder	Obesity	21–49	1–2
	Diabetes	8–17	1.5–2
	Hypertension	35–61	2–3
	Dyslipidemia	23–38	≤3
	Metabolic syndrome	30–49	1.5–2

Reproduced, with formatting modifications, from de Hert et al. (2009).[2]

discussion could also conceptually include posttraumatic stress disorder, borderline personality disorder, obsessive-compulsive personality disorder, major depressive disorder, and other psychiatric conditions that involve physiological recalibrations. Here we chose to focus exclusively on schizophrenia and bipolar disorder as SMI because they are disabling psychiatric conditions requiring extensive treatment and rehabilitation that often entail careful monitoring of many biomarkers used to measure AL.

ALLOSTASIS AND ALLOSTATIC LOAD

The term *allostasis* describes the adaptive physiological responses that organisms activate when homeostasis is disrupted.[9] Unlike homeostasis, where the body secures optimal functioning of the internal milieu through consistency of local feedback mechanisms, allostatic processes alter metabolic functioning via optimal compensatory and anticipatory mechanisms responsive to environmental demands. As an example of allostasis, Sterling and Eyer[9] used shifts in blood pressure set points and asked: how could homeostasis account for day-to-day variations in blood pressure, given the moment-by-moment fluctuations that occur in so many different contexts?

To answer such questions, the allostatic concept implicates the whole brain and body rather than the simple local feedback loops characteristic of homeostasis.[10] If there were such a thing as a homeostatic blood pressure set point, our levels would invariably be too low or too high to match resources to the needs of the situation (e.g., blood pressure rises more during sexual activity than during sleep). In this vein, Sterling and Eyer[9] postulated that age-related increases in blood pressure and that differences between socioeconomic strata could be viewed as physiological recalibrations matched to situational needs. The general goal of allostasis is therefore to direct compensatory mechanisms in bodily functions in order to promote adaptation to environmental changes.

We can use the example of blood pressure to illustrate three of the main limitations of traditional homeostatic theory, all of which are addressed by the concept of allostasis. First, homeostasis operates by shutting down overactive biological systems that function according to static set points. Such activity does not account, however, for the dynamic process whereby the matching of needs to demands recalibrates set points to maximize the organism's resources (e.g., increased blood pressure during strenuous physical activities). Second, when increased needs create an error signal, negative feedback mechanisms may try to correct the error ineptly (e.g., head rush when standing too swiftly). Neurological modulation and anticipation of physiological phenomena, however, can change behaviors to meet specific

Table 2
Causes of Premature Mortality Among Medicated Schizophrenic and Bipolar Patients

Condition	Causes of mortality	Standardized mortality ratio compared to general population
Schizophrenia	All causes	2.98
	Cardiovascular	2.01
	Cerebrovascular	0.87
	Neoplasm	1.44
	Suicide	43.47
Bipolar disorder	All causes	1.58
	Cardiovascular	1.84
	Cerebrovascular	1.37
	Neoplasm (tumors)	0.84
	Suicide	12.28

Source: For schizophrenia, data are based on a meta-analytic study by Saha et al. (2007).[3] For bipolar disorder, data are based on national Swiss surveys reported by Angst et al. (2002).[4]

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needs (e.g., rising slowly to avoid head rush). Third, and most notably for biomedicine, homeostatic models define health as a state in which all physiological parameters have normal values or ranges; values outside that range need to be corrected and may be used to warrant pharmaceutical intervention (e.g., for hypertension).

By contrast, allostasis defines health as a state of optimal predictive fluctuation in response to the demands of the environment. Sterling and Eyer[9] argued that medical practices based on homeostatic definitions have an iatrogenic potential—that is, treatments based on such definitions may themselves cause medical problems—and can result in polypharmacy. In this scenario, successive treatments are added to address problems arising when correcting one parameter causes other systems to become dysregulated.[10] In sum, allostasis differs from homeostasis by emphasizing dynamic set points, taking into account the brain's broader role in feedback regulation, and conceptualizing health as a multifaceted adaptation to contexts.[7,11]

The physiological changes associated with chronic stress represent a powerful example in which allostatic adaptation leads to pathogenic maladaptation. During acute stress, real or interpreted threats to homeostasis initiate the sympathetic-adrenal-medullary (SAM) axis release of catecholamines and the hypothalamic-pituitary-adrenal (HPA) axis secretion of glucocorticoids in order to mobilize energy that fuels adaptive fight-flight-freeze responses.[12] When chronically activated, these allostatic mechanisms become physiologically taxing and constitute an AL as one's susceptibility to stress-related disease increases:[13] AL is the physiological price of adaptation that organisms pay when allostasis is repeatedly activated over extended periods of time.[14]

The development of a simple AL algorithm has led to a useful multisystemic AL index[5] that incorporates the synergistic effects of numerous biomarkers predictive of pathological states.[15] Specifically, count-based AL indices have been created to represent multiple biomarkers that are dichotomized according to subclinical and clinical thresholds[5] based on the sample's distribution for a specific biomarker. An individual's values falling into high-risk quartiles (e.g., the 75th percentile or above for adrenalin, or 25th percentile or below for dehydroepiandrosterone sulphate) are coded as "1" and those within normal ranges as "0," and these outcomes are then summed into an AL index that is used to predict health outcomes. Figure 1 compiles the most frequently reported biomarkers based on approximately 60 studies that incorporated AL algorithms.

Substantial evidence shows that AL indices predict numerous stress-related health outcomes.[7] Specifically, higher ALs based on ten biomarkers corresponded to lower baseline functioning, poorer cognitive performance, and weaker physical performance cross-sectionally.[17] Furthermore, longitudinal follow-ups of the MacArthur cohort of successful agers showed associations between higher ALs and increased risk of cardiovascular disease and all-cause mortality.[18,19] These findings have been replicated cross-culturally using a Taiwanese cohort.[20–24] Encouragingly, decreases in AL over two to four years reduce mortality rates.[25] Notwithstanding, no studies have yet to assess AL-focused interventions in the general population.

Based on a review of approximately 60 studies,[7] increased AL indices correspond either cross-sectionally or longitudinally to a plethora of antecedents (e.g., socioeconomic disadvantage, poor social networks, workplace stress, maladaptive personality traits, particular lifestyle behaviors, genetic polymorphisms) and consequences (e.g., mortality, cardiovascular disease, psychiatric symptoms, cognitive decline, physical/mobility limitations, neurological atrophy). To date, no studies have employed AL algorithms in relation to individuals afflicted with bipolar disorder or schizophrenia. Because the predictive power of AL has been successfully validated in unaffected populations, we believe that measuring AL among patients with SMI will give medical professionals insights into distinct biological signatures predictive of comorbidities.

PHYSIOLOGICAL DYSREGULATIONS AND COMORBIDITIES IN SEVERE MENTAL ILLNESS

As reported in Tables 1 and 2, SMI are associated with physical morbidities and reduced life expectancy among medicated patients.[26–28] Schizophrenic and bipolar patients have a 1.5- to 3-fold increased mortality rate compared to the nonpsychiatric population, and these statistics have worsened over the last decades.[3,29] According to a meta-analysis, suicides and accidents (28% for schizophrenic patients and 12% bipolar patients) largely account for this higher mortality rate.[27] Yet the most common cause of death in SMI patients is cardiovascular disease.[27,28,30] Patients with SMI are more likely to have common risk factors for cardiovascular disease such as obesity and smoking. Furthermore, the diabetes rate is 2–3 times higher than in the general population[31,32] and affects 10%–15% of schizophrenic and bipolar patients. Many of these physical comorbidities are related to physiological dysregulations conceptualized and consistently observed in the AL literature.[6]

Multiple allostatic mediators representing neuroendocrine, immune/inflammatory, metabolic, and cardiovascular function are part of a nonlinear network that contributes to stress-related diseases.[33,34] First, over-activation of *primary mediators* such as stress hormones (e.g., cortisol, adrenalin, dehydroepiandrosterone) and pro- and anti-inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor–alpha) exacts *primary effects* on cellular activities. Second, subsidiary systems, in turn, recalibrate their own cellular activities to compensate for the over- or underproduction of primary mediators. This process leads to *secondary outcomes*, whereby metabolic (e.g., cholesterol, insulin), cardiovascular (e.g., blood pressure, heart rate variability), and second-order immune (e.g., c-reactive protein, fibrinogen) biomarkers

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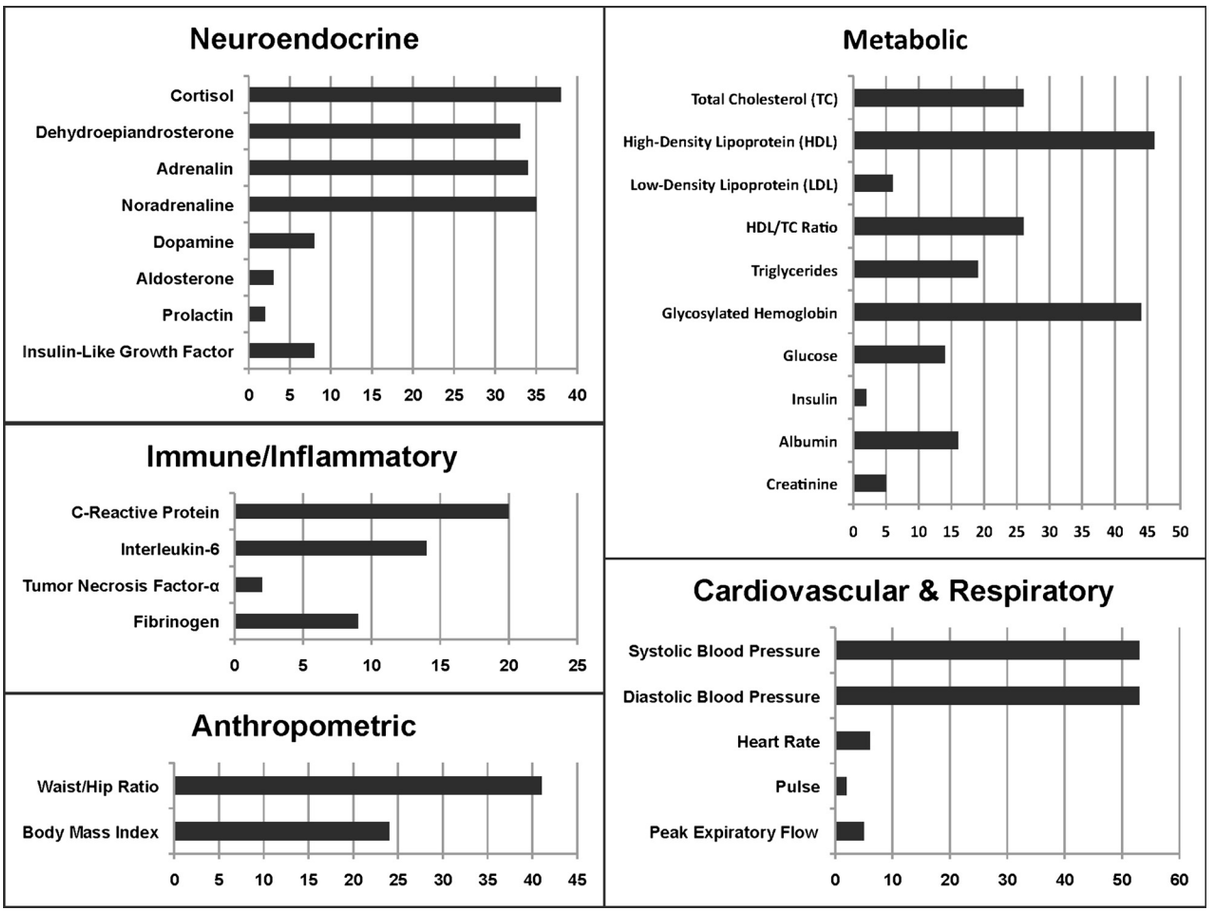

Figure 1. Frequency of studies using specific biomarkers of allostatic load as incorporated into allostatic load algorithms (based on approximately 60 reports).[7,16]

become dysregulated. Finally, *tertiary outcomes*, manifesting in clinical endpoints (e.g., cardiovascular disease, diabetes, mortality), signal a pathological degree of AL.

In the context of the present discussion of SMI, neuroendocrine and immune dysregulations are pronounced in schizophrenia and bipolar disorder (see Tables 3 and 4).

Based on such examples, it appears that patients with schizophrenia or bipolar disorder, as well as those with mood disorders, may experience an ongoing hypercortisolism and pro-inflammatory syndrome. It is difficult to distinguish, however, between the relative influence of pathophysiological mechanisms inherent to SMI and other factors that influence neuroendocrine and cytokine levels, such as adiposity and interactions with medications and other biomarkers.[54,55] Investigations of individual AL biomarkers and clusters thereof demonstrate that, compared to controls, bipolar patients are at increased risk of cardiovascular disease and hypertension,[56] and that bipolar women are at increased risk of obesity even in the absence of insulin resistance.[57] Strikingly, 30% to 40% of bipolar patients meet criteria for metabolic syndrome.[58,59]

The above problems of patients with SMI have multifaceted etiological underpinnings (e.g., genetics, early life adversities, lifestyles, medications) that are intricately linked to AL.[60] It is important to highlight that, while the AL model has been investigated generally as a predictor of physical outcomes like cardiovascular disease in aging studies, research also links it to cognitive and psychiatric problems particularly relevant to the study of SMI. Indeed, pathophysiologies overlap among physical and psychiatric conditions.[61]

Psychiatric comorbidities in SMI are important to consider in relation to the AL model (see Figure 2). Lifetime psychiatric comorbidities are remarkably high and associated with earlier onsets, worse disease course, and poorer treatment adherence.[62–64] The most commonly shared psychiatric comorbidities among schizophrenic and bipolar patients are substance abuse and anxiety disorders.[62,63] For example, approximately 50% of schizophrenic patients[65] and 60% of bipolar patients[63] abuse substances. Indeed, a rich theoretical literature linking AL to substance abuse,[66–71] mood disorders,[8,72–75] and anxiety disorders[76–78] further suggests that AL is associated with various psychopathologies

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Table 3
Physiological Dysregulations in Allostatic Load Mediators in Schizophrenia and Bipolar Disorder

Biomarker	Schizophrenia	Bipolar disorder
Cortisol (basal peripheral levels)	Drug-naive first-episode patients: ↑ levels[35,36] Medicated patients: ↑ levels[37,38] Chronic patients: ↑ levels[39]	Patients: ↑ levels[37,40]
Cortisol (pharmacological challenge)	↑ dexamethasone suppression test reactivity[a,41] ↓ dexamethasone suppression test reactivity[a,42]	All illness phases: ↑ dexamethasone suppression test reactivity[43,44] Patients in remission at risk of depressive relapse: abnormal reactivity to CRH challenge test[45]
DHEA	Chronic patients: DHEA-to-cortisol ratio is negatively correlated with the duration of illness[46]	Normal DHEA levels[37]
Cytokines	↑ IL-6, ↑ IL-1RA, ↑ soluble IL-2R & ↓ secretion of IL-2 by peripheral blood leukocytes[47]	↑ IL-1R, ↑ IL-2R, ↑ IL-4, ↑ IL-6, ↑ IL-8 & ↓ IL-2[48–53]

CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; IL, interleukin; R, receptor; RA, receptor agonist.
[a] Mixed dexamethasone suppression findings may be attributable to differential (1) baseline levels of plasma cortisol and serotonin among schizophrenic patients manifesting increased reactivity[41] and (2) comorbid diagnosis of depression among schizophrenic patients manifesting decreased reactivity.[42]

in addition to the pathophysiologies originally investigated, such as cardiovascular disease. Moreover, anxiety disorders can represent important risk factors for developing bipolar disorder[79] and can co-occur with eating disorders in patients with subsyndromal symptoms following an acute episode.[80]

The prevalence of such comorbidities points to common pathways of physiological dysregulation. If the AL model can demarcate vulnerabilities among healthy adults and successful agers, then future investigations among SMI populations may show promise as a multi-analytic approach to monitoring disease trajectories.

Further research will undoubtedly increase our understanding of comorbid manifestations and eventually lead to improved prediction of disease onset or recurrences, and also to individualized treatment approaches.[61] The concepts of allostasis and AL represent useful ways to identify inter-individual predispositions among common mechanisms that contribute to stress-related outcomes relevant to psychiatry.[60]

BEHAVIORAL COMPENSATION AND COGNITIVE IMPAIRMENTS IN SEVERE MENTAL ILLNESS

Allostatic regulatory systems interact in a hierarchical, dynamic, and nonlinear manner in response to stressors—which prompts compensatory behaviors. From this perspective, lifestyle choices of SMI patients can be considered as "higher-order" allostatic mechanisms activated in reaction to external and internal cues. As such, maladaptive behaviors have the propensity of increasing AL levels even further. For instance, changes in eating behaviors may be compensatory in nature among conditions that alter the

Table 4
Inflammatory Markers Among Bipolar Patients During Mania Versus When Depressed

Biomarker[a]	Mania	Depression	Observation/reference
IL-1RA	↑		Statistically higher in remitted patients[50]
IL-2	↓	↓	Ortiz-Dominguez et al. (2007)[52]
IL-2R	↑	↑	Positively correlated to the severity of manic symptoms[48,53]
IL-4		↑	Ortiz-Dominguez et al. (2007)[52]
IL-6	↑	↑	Returned to baseline in response to stabilizers[49,51,52]
IL-8	↑	↑	O'Brien et al. (2006)[51]
IL-10	=	=	O'Brien et al. (2006)[51]
TNF-α	↑	↑	Kim et al. (2007),[49] O'Brien et al. (2006),[51] Ortiz-Dominguez et al. (2007)[52]

IL, interleukin; R, receptor; RA, receptor antagonist; TNF-α, tumor necrosis factor–alpha.
[a] IL-1RA, IL-6, and TNF-α are considered to be prominent pro-inflammatory cytokines, whereas IL-4 and IL-10 act as anti-inflammatory cytokines.

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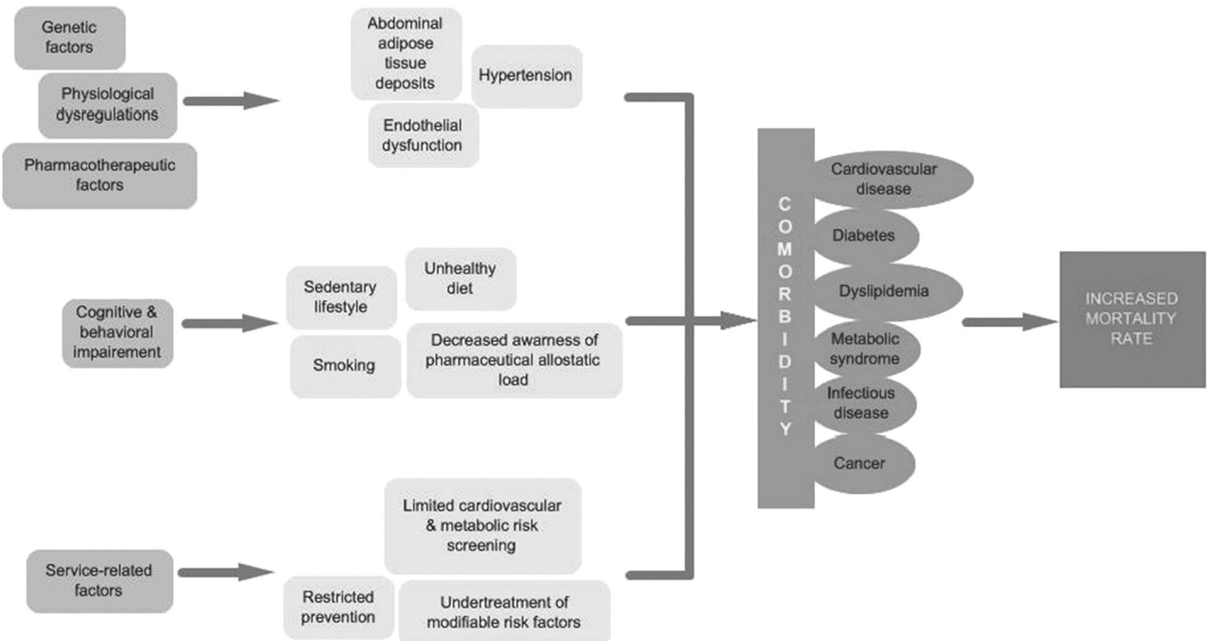

Figure 2. Pathways to comorbidity and mortality in schizophrenia and bipolar disorder. Central to every domain depicted are the direct and indirect effects of chronic stress and concomitant mediators of allostatic load.

brain reward system.[81] "Self-medication" by overeating may, for example, dampen stress-induced negative affect. Indeed, depressed individuals who overeat show reduced concentrations of both cerebrospinal corticotropin-releasing hormone and catecholamine that counteract distressing affects.[82]

In parallel, cognitive dysfunction can modulate behavioral compensations (for a recent AL review of clinically important cognitive impairments among bipolar patients, see Vieta et al.).[83] Of particular importance are the reciprocal interactions among cognitive and behavioral impairments that further contribute to AL and subsequent morbidities. Cognitive impairments may represent an outcome of sustained AL or may perhaps be an indirect consequence of behavioral compensation to which sustained AL contributes.

Deficient reward pathways have been identified in both schizophrenia[81] and bipolar disorder.[84] This deficiency may be due to abnormal motivational states referred to as *aberrant salience attributions*,[85–87] together with a lack of reactivity to normally rewarding stimuli,[88,89] itself the result of altered mesolimbic dopaminergic circuitry. Notably, these factors may explain the preference for highly salient cues, such as fast foods and illicit substances.[81] As will be described further on, a similar mechanism has been proposed to mediate the vulnerability to addiction in schizophrenic patients.

The rate of obesity, which represents a major risk factor for a range of chronic medical conditions,[90] is substantially higher in SMI patients than in the general population.[91] Although psychotropic medications explain a large portion of weight gain in psychiatric populations, dietary habits remain an important contributing factor for obesity. Indeed, SMI patients report diets that are rich in saturated fat[92] and carbohydrates,[93] and scarce in fruits and vegetables,[94] and they also report increased overall caloric intake (due to overeating).[95] Of particular relevance is that a diet rich in saturated fats and sugar—two elements representing important sources of AL—is associated with worse clinical outcomes in schizophrenia.[95] Also interesting is that high-calorie diets—in particular, high-fat diets—may increase the production of reactive oxygen species associated with mitochondrial activities, which may lead to insulin resistance and other deleterious cellular metabolic consequences.[96,97]

Other behaviors that increase AL in SMI patients include smoking and the use of alcohol and illicit substances—which can act as forms of self-medication secondary to core psychopathological symptoms and medication side effects. The mechanisms underlying the greater propensity to abuse substances in schizophrenia is not completely understood, but mesolimbic, dopamine-mediated reward regulation is clearly implicated.[98] Unfortunately, addictive behaviors worsen with stress and clinical instability in schizophrenic patients. Moreover, patients have a tendency to overvalue immediate rewards and devalue delayed punishments.[99] Data from animal research indicate that the regulation of addictive behaviors and the stress response share a common set of genes,[100] suggesting a mechanistic coupling between stress reactivity and addiction.

Addictive behaviors are significant problems for SMI populations because of downstream clinical consequences

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that further interact to precipitate comorbidities. For example, smoking, which increases the incidence of lung disease and cancer, reaches a prevalence of 50%–80% in schizophrenic patients and 54%–68% in bipolar patients, representing a 2- to 3-fold higher prevalence than in the general population.[101] Lifetime incidence of substance misuse or dependence exceeds the prevalence observed in the general population and all other Axis I psychiatric diagnoses: in the United States it is estimated to be as high as 47% in schizophrenia and 61% in bipolar disorder.[65] Alcohol represents the most commonly abused substance, followed by cannabis and cocaine.[102]

Several neurological factors contribute to the higher prevalence of smoking in schizophrenia. For instance, cholinergic and nicotinic neurotransmission are associated with smoking rates.[103] Post-mortem studies of schizophrenic patients reveal decreased nicotinic receptor density in the hippocampus,[104] and malfunctioning of the alpha-7 subunit of the nicotinic acetylcholine receptor is involved in nicotine's positive effects on memory function[105] and its positive impact on sensory gating,[106] attention,[107] and memory,[108] which suggests that smoking may be used to remediate cognitive disability.[109] Nicotine also activates the mesolimbic reward dopaminergic pathway in animal models[110] and contributes to the alleviation of negative affective symptoms in depressed[111] and schizophrenic[112,113] patients. Smoking byproducts might also increase drug metabolism and thus reduce the plasma concentrations of certain antipsychotic medications,[114] thus decreasing side effects.

Another clinically relevant issue in schizophrenic populations is increased caffeine intake.[115,116] High levels of caffeine may exacerbate psychiatric symptoms[116] and medication side effects by increasing antipsychotic plasma levels.[117] As in smoking, the overuse of caffeine may serve to palliate dysfunction through beneficial effects on alertness, cognition, and mood,[118] due in part to indirectly increased dopamine neurotransmission.[119] It is worth mentioning that caffeine intake correlates with daily smoking rates in schizophrenic patients but not in normal individuals,[120] indicating a possible cross-sensitization effect involving nicotine-responsive neural pathways and schizophrenic psychopathology. Although illness-related behaviors are similar in schizophrenia and bipolar disorder, research investigating underlying neurobiological mechanisms has been predominately performed in schizophrenic individuals, ultimately limiting the conclusions we can draw now for patients with bipolar disorder.

The significance of illness-related behaviors in SMI extends far beyond lifestyle choices. Lowered social adaptability and altered motivation for help seeking in SMI patients strongly influence compliance with psychiatric treatments and appropriate treatment of somatic complaints. Hence, schizophrenic and bipolar patients may become further disadvantaged compared to mentally healthy individuals, and may even be overlooked by the health care system.[121–123] Reasons may include poor personal care and also physiological disturbances. For instance, schizophrenic patients are less sensitive to somatic problems because of an increased pain tolerance related to abnormal opioidergic functioning that is further blunted by antipsychotic medication.[81]

Together with cognitive impairment and behavioral overcompensation, lower pain sensitivities may decrease the ability to express somatic complaints.[124] These factors may lead to more somatic disorders in SMI patients due to an overall decreased awareness of acute symptoms. This decreased awareness represents compromised functioning of allostatic mechanisms since unaffected individuals would respond to pain by adapting their behavior to reduce discomfort. These findings indicate that in both clinical and research settings, SMI patients' cognitive and behavioral aspects must be taken into account as confounders that could significantly influence the patient's symptoms, compliance, biological functioning, disease progression, and development of comorbidities.

Taken together, unhealthy lifestyle behaviors may represent behavioral compensatory mechanisms used to counteract negative affective states related to inherent neurobiological predispositions. Such behaviors are, in effect, allostatic mechanisms because they compensate for dysfunction, though ultimately at the expense of long-term health. Therapeutic interventions that target specific neural pathways or that aim to replace damaging behaviors with less or nondamaging ones (e.g., physical exercise, dietary restriction) would therefore be beneficial.

PHARMACOTHERAPY, IATROGENIC EFFECTS, AND PHARMACOLOGICAL ALLOSTATIC LOAD

The treatment of schizophrenia and bipolar disorder involves an integrated approach resting on a foundation of pharmacological interventions. The pharmacopeia used to treat these disorders includes first-generation, or typical, antipsychotics (FGAs), second-generation, or atypical, antipsychotics (SGAs), traditional mood-stabilizing agents (lithium and anticonvulsants), and antidepressants (selective serotonin reuptake inhibitors and tricyclics). Variations in chemical structure, physiological effects, and clinical relevance are important even within a particular pharmacological class of drugs. Several levels of interplay exist between psychotropic treatment effects and allostatic mechanisms, including HPA-axis reactivity, immune regulation, neuroplasticity, cognitive functions, metabolic regulation, and unhealthy behaviors. Findings indicate that pharmacological interventions may decelerate, halt, or even reverse the detrimental cognitive processes found in SMI. Unfortunately, when pharmacological treatment can alleviate clinical symptoms, it can also aggravate the course of illness in the form of diverse negative sequelae.

Treatment of SMI with many of the currently preferred pharmacological agents can inadvertently increase

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the chances of developing AL secondary outcomes, largely in the form of metabolic comorbidities. First and foremost, many of the atypical antipsychotics are associated with an increased risk of developing metabolic syndrome (via weight gain), abnormalities in blood lipid profiles, insulin resistance, and type 2 diabetes.[125] Atypical antipsychotic agents differ significantly in their potential to cause clinically relevant weight changes (>7% increase); clozapine, olanzapine, and quetiapine are the agents with the highest risk.[126]

Several mechanisms have been proposed to explain weight gain related to antipsychotic treatment. First, the receptor profile of antipsychotics can increase appetite,[127,128] with different receptor types implicated.[81] In this context, specific polymorphisms may augment the risk of weight gain in interaction with specific antipsychotic agents, as is the case for polymorphisms of the serotonin 2C receptor gene and olanzapine.[129] Second, due to their sedative effects, antipsychotics contribute to diminished physical activity and subsequently decreased energy expenditure.[125] For a constant dietary/energy intake, reduced energy expenditure induces a state of metabolic oversupply that favors weight gain, insulin resistance, and increased susceptibility to age-related diseases.[130] Whereas physical activity promotes healthy effects by triggering mitochondrial biogenesis and antioxidant and anti-inflammatory processes, physical inactivity and overeating have the opposite effects.[130,131] More broadly, physical inactivity and adiposity in the general population have been associated with poor overall health and higher levels of several chronic and age-related illnesses,[132,133] including cognitive decline and dementia.[134,135] Finally, SGAs can further impair preexisting hedonic disturbances of the opioidergic system in schizophrenic patients.[81]

Given, however, that no weight gain is observed in about 25% of cases of the metabolic syndrome during antipsychotic treatment, other mechanisms are likely to be contributing to the metabolic disturbances.[136] A Finnish cohort study concluded that patients on antipsychotic medications were three times more likely than nonmedicated controls to have elevated cholesterol and triglyceride profiles.[137] In two comprehensive reviews of atypical antipsychotics,[136] it was concluded that the relative risk for hyperlipidemia is highest for clozapine and olanzapine, inconsistent for quetiapine, and lowest for risperidone, with ziprasidone and aripiprazole being comparatively neutral.[138] In addition to altering lipid profiles, antipsychotics may directly affect pancreatic functions and induce reversible glucose abnormalities.[126]

Data regarding adverse metabolic effects of mood stabilizers and antidepressants are currently less abundant. Nonetheless, treatment with major mood stabilizers—for example, lithium,[139] valproate, and carbamazepine[140]—is associated with weight gain. Preliminary data also suggest that antidepressant treatment is more common in diabetic populations.[141] In considering this vast array of side effects that essentially contribute to physiological dysregulations and combordities, the AL model could be used to monitor pharmaceutical recalibrations that precipitate deleterious behavioral compensations (e.g., substance abuse, overeating) in SMI.

In addition to these negative physiological effects, several psychotropic agents seem to interact with illness-related predispositions to synergistically worsen some unhealthy lifestyle behaviors and ultimately induce a "pharmacological" AL. As first described elsewhere,[60] we define *pharmacological AL* (PAL) as the adverse iatrogenic effects that medications can exert that then inadvertently prompt individuals to remediate the biological system(s) affected by unhealthy means. For example and as depicted in Figure 3, smoking is often used to dampen adverse side effects of antipsychotic medications, but the smoking further amplifies AL levels. Such behavioral side effects represent maladaptive allostatic mechanisms whereby patients strive to re-regulate medicinally altered neurotransmitter functions linked to cognition and motivation. For instance, smoking may be used to re-regulate the alteration of reward mechanisms that are modulated by the dampening of mesolimbic dopaminergic functioning via antipsychotics (see Figure 3).

In terms of a patient's subjective experience, prominent antipsychotic side effects interfere with mood and the ability to be alert and derive pleasure from routine life experiences. Specifically, antipsychotic drug treatment is reported to provoke (1) neuroleptic dysphoria,[142,143] primarily via high D2 blocking agents, (2) sedation/drowsiness that impairs judgment, thinking, or motor skills,[125,144] (3) altered reward functions,[145,146] and (4) misbalanced dietary preferences.[81] We propose that using AL indices could provide insights into PAL. This concept goes beyond the known side effects of psychopharmacology: it endeavors to understand how drugs meant to treat primary diagnoses inadvertently prompt physiological dysregulations and comorbidities via patients' behavioral compensations.

A number of preclinical studies provide neurobiological support for the PAL concept via multiple systems affected both directly and indirectly by medications or by psychopathological neural processes. Several lines of evidence point to three major neurochemical effectors of PAL: the (1) dopaminergic, (2) cholinergic, and (3) opioidergic systems.

The central pharmacodynamic property shared by currently available antipsychotic agents is dopamine D2 receptor blockade. Antipsychotic effects vary according to the level of D2 receptor occupancy.[147] While occupancy thresholds above approximately 60% are necessary for a satisfactory response,[148,149] side effects such as extrapyramidal symptoms (i.e., akathisia, dyskinesia, dystonia) or hyperprolactinemia emerge when the occupancy reaches 78% and 72%, respectively.[150] Furthermore, negative effects on subjective experience may appear even before the threshold for other side effects has been reached,[145,147] and likely reflect excessive inhibition of dopamine neurotransmission in the striatal, temporal, and insular regions[145] involved in

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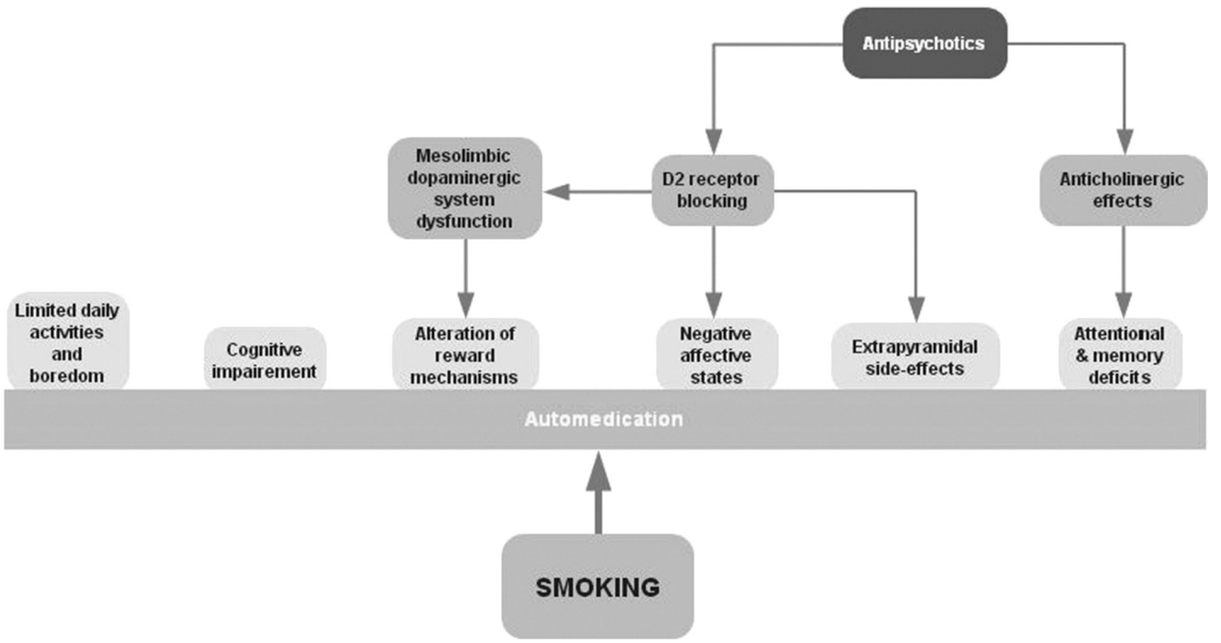

Figure 3. Smoking as an example of pharmacological allostatic load. Smoking is used to self-medicate against symptoms iatrogenically induced by prescribed antipsychotic medications.[60]

reward and motivation (ventral striatum) and in affective regulation and awareness of internal feelings (temporal and insular structures). Interestingly, neuroleptic dysphoria has been proposed to be one of the missing links between schizophrenia and substance abuse,[142] as these patients are more likely than nondysphoric patients to develop comorbid drug abuse.[151]

The differential capacities of FGAs and SGAs to induce dopamine deficits seem to be clinically important. For example, lower rates of substance abuse are found among patients treated by clozapine (an SGA) compared to FGAs.[152] Furthermore, D2 receptor blocking in the striatum might increase the risk of addictive behaviors,[99] and chronic blockade of D2 receptors may reinforce the addictive behavior via upregulated postsynaptic dopamine receptor functioning, as evidenced in animals chronically treated with haloperidol.[153]

Following this line of reasoning, we hypothesize that the misuse of illicit substances constitutes an allostatic mechanism meant to restore pharmacologically dampened dopaminergic transmission. For instance, in a case study of a schizophrenic patient, cannabis enhanced synaptic dopaminergic neurotransmission.[154] Similarly, amphetamine[155,156] and cocaine[157] are known to exert their effects through dopamine enhancement, and cortisol secretion is stimulated by delta-9-tetrahydrocannabinol, the active agent in cannabis,[158] as well as by amphetamines.[159,160] Chronic consumption of these drugs may therefore contribute to dysregulations of the HPA axis in a reciprocally damaging manner. By comparison, pharmacological studies in healthy samples reveal that haloperidol (an FGA and potent D2 receptor antagonist) causes psychomotor slowing and impaired executive function[161] as well as sustained attention deficits and decreased self-reported quality of life.[162]

Pharmacological D2 receptor modulation also worsens preexisting vulnerabilities toward increased tobacco smoking in psychiatric patients. In a prospective study, the potent D2-receptor-blocking FGAs were associated with an increase in nicotine dependence, which was not the case for SGAs.[163] Consistently, occupancy of D2 receptors positively correlates with the number of cigarettes smoked in young schizophrenic patients, with significant differences in the percentages of D2 receptor occupancy for smokers (mean = 74.3%) and nonsmokers (mean = 49.8%).[164] Interestingly, treatment with aripiprazole, a partial agonist of the D2 receptor, reduces both nicotine dependence and cigarette cravings.[163] Similarly, patients treated with clozapine display lower rates of smoking and higher rates of smoking cessation than those treated with FGAs.[165]

Preclinical research studies have found nicotine-mediated increases of dopamine transporters in the ventral tegmental area[166] and prefrontal cortex,[167] which provides additional insights into complex interactions between the nicotine and dopamine circuitry implicated in cognition and motivation. It is noteworthy that nicotine has the potential to alleviate several physical side effects related to D2 receptor blockade.[168–170] In animal models, nicotine has a powerful preventive effect on the neuroleptic-induced dopamine D2 receptor upregulation[171] associated with extrapyramidal symptoms.[172] A similar finding was shown in a human

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case-control study involving schizophrenic patients under chronic antipsychotic treatment.[171] These results suggest that patients' motivations toward maladaptive behaviors and substances that influence dopamine production—for example, smoking—might represent a form of PAL related to antipsychotic medications.

Evidence for PAL could arise from activity of cholinergic circuitry (e.g., nicotinic and muscarinic receptors) in relation to memory and attention. Many psychotropic agents are known to antagonize muscarinic receptors[173] and can inadvertently induce cognitive perturbations.[173] Some researchers have proposed that clinical and pharmacological anti-cholinergic indices be used in conjunction with neuropsychological assessments in order to monitor cognitive deficits.[174] These iatrogenic impairments exacerbate the preexisting perturbations of the cholinergic system found in schizophrenic patients (as discussed earlier). Importantly, nicotine can counteract these PAL-induced cognitive dysfunctions,[175,176] which can prompt patients treated with medications that have anti-cholinergic effects to use this addictive and toxic substance as an antidote. It should be noted, however, that similar self-medication hypotheses have been questioned by several studies and therefore remain open to debate.[177,178]

Analgesic pharmacological properties reported in both animal[179–181] and human[182–184] studies suggest that some SGAs (clozapine, olanzapine, risperidone, and amisulpride) may increase opioidergic neurotransmission. As reviewed previously,[81] SGAs may worsen preexisting elevations of endogenous opiates inherent to schizophrenia,[185] which might, in turn, alter the "likability" processes of this reward pathway, leading to hedonic preferences for sweet and fatty foods.[186,187] The interplay between the opioidergic system and antipsychotic action might also be relevant in more classic addictive behavior; for example, the administration of naltrexone (an opioid antagonist) to alcohol-abusing patients with schizophrenia decreased consumption.[188]

Given the differences among specific agents and dosing regimens, coupled with the overall paucity of evidence, we need to be cautious in drawing conclusions. Nevertheless, it can be postulated that interactions between psychotropic drugs and several important neurobiological mechanisms might drive PAL effects. At the heart of the three neurochemical systems involved in PAL presented in this review are interactions that regulate HPA axis activity by further dampening cortisol dynamics associated with SMI and the medications used to treat them.

In sum, PAL can be understood as inducing maladaptive behaviors that ultimately disrupt AL primary mediators (e.g., stress hormones, cytokines) and effects (e.g., cellular activities), as well as secondary outcomes (e.g., traditional biomedical markers representing metabolic and cardiovascular systems), that finally culminate in comorbidities or tertiary outcomes (e.g., metabolic syndrome). We propose that using the AL model to interpret the results of standard laboratory reports can provide medical professionals with a sensitive tool to monitor patients' global responses to treatment. The PAL concept also constitutes an advantage compared to focusing solely on numerous known side effects because it provides a global measure that subsumes the effects of various phenomena, including the primary pathology, treatment, its side effects, and maladaptive compensatory behaviors, as well as other unidentified contributors to AL. Given that many of the biomarkers collected in routine blood work are the same as those used in constructing AL indices (see Figure 1), applying a simple calculation could be easily integrated into a typical clinical follow-up. AL indices can also serve as a starting point for a discussion between the patient and the health practitioner regarding adaptive behaviors and prevention of negative sequelae related to the illness and its treatment.

CLINICAL ALLOSTATIC LOAD INDEX FORMULA FOR MEDICAL PRACTITIONERS

The AL index is thus far a research tool with the promising possibility of becoming a clinical tool.[60] More work is needed for it to become accessible and useful to medical practitioners. Studies including AL indices have typically based cutoffs on the sample's distribution for a given biomarker; such an approach, however, does not lend itself well to clinical practice. The following simple formula generates an AL index based on clinical reference ranges used routinely for diagnostic purposes.[16] For each biomarker value included, a subclinical cutoff can be easily calculated based on normative clinical ranges accompanying biomarker results.

Let us consider, as an example, total cholesterol with a normal range between 3.3 and 5.2 nmol/L. First, to determine the *range*, subtract the lower limit from the upper limit (5.2 – 3.3 = 1.9). Second, to determine the *quartile*, divide the range by four (1.9/4 = 0.475). Third, to determine the *cutoff*, either subtract the quartile from the upper limit for the upper cutoff (5.2 – 0.475 = 4.725) or, in the case of biomarkers like HDL-cholesterol, DHEA-S, and albumin whereby lower levels are deleterious, add the quartile to the lower limit for the lower cutoff (3.3 + 0.475 = 3.775). Based on this example, a patient with total cholesterol at 4.725 nmol/L or higher would get a score of 1, whereas values below this cutoff would be scored as 0. A clinical AL index is therefore the sum of subclinically dysregulated biomarkers for each individual. Figure 4 extends this approach to 14 biomarkers commonly used in AL studies. While this formula is designed for medical practice, it does not yield cutoffs that are much different from those using biomarker distributions based on the sample distributions generally used in empirical AL studies.[16]

Calculating a clinical AL index to monitor comorbidities could also help identify specific biological systems associated with unique clinical manifestations and to then tailor

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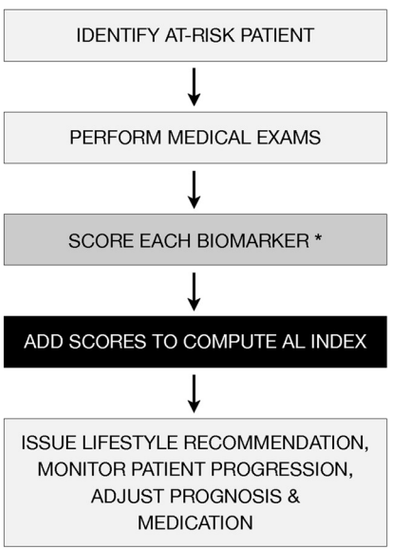

* BIOMARKER	NORMAL RANGE	LOWER LIMIT (25th percentile)	HIGHER LIMIT (75th percentile)
Cortisol	166 - 828 nmol/L	≤ 331.5 → **0**	≥ 662.5 → **1**
Dehydroepiandrosterone-sulphate	0 - 18.7 µmol/L	≤ 4.68 → **1**	≥ 14.03 → **0**
Insulin	0 - 100 pmol/L	≤ 25 → **0**	≥ 75 → **1**
Glycosylated hemoglobin	0.046 - 0.062 %	≤ 0.05 → **0**	≥ 0.058 → **1**
Total cholesterol	2.8 - 5.2 mmol/L	≤ 3.40 → **0**	≥ 4.60 → **1**
High density lipoprotein cholesterol	0.9 - 2.0 mmol/L	≤ 1.18 → **1**	≥ 1.73 → **0**
Triglycerides	0.4 - 1.8 mmol/L	≤ 0.75 → **0**	≥ 1.45 → **1**
Albumin	32 - 46 g/L	≤ 35.5 → **1**	≥ 42.5 → **0**
C-reactive protein	0 - 8 mg/L	≤ 2 → **0**	≥ 6 → **1**
Fibrinogen	2 - 4.8 g/L	≤ 2.7 → **0**	≥ 4.10 → **1**
Systolic blood pressure	90 - 140 mmHg	≤ 102.5 → **0**	≥ 127.5 → **1**
Diastolic blood pressure	60 to 90 mmHg	≤ 67.5 → **0**	≥ 82.5 → **1**
Waist-to-Hip ratio	0.8 - 1	≤ 0.85 → **0**	≥ 0.95 → **1**
Body mass index	18.5 - 25	≤ 20.125 → **0**	≥ 23.375 → **1**
ALLOSTATIC LOAD INDEX	**N/A**	**→ 3**	**+ → 11 = 14**

Figure 4. Clinical approach to calculating and interpreting allostatic load indices. Upon identifying patients at high risk of developing comorbidities, an allostatic load index can be easily calculated based on clinical norms for biomarkers routinely collected.[7,16] The 14 biomarkers listed here as examples come from a previous study of workplace stress that introduced a clinical allostatic load index formulation. In the formulation used here, a one-tailed approach is applied using either the lower limit or the higher limit to denote risk. For some biomarkers, however—such as serum cortisol, as measured here—a two-tailed approach could be set at the 12.5th and 87.5th percentile to denote risk attributable to hypo- and hypercortisolism. Note that the clinical norms will change according to the biochemical assays used, the vehicle collected (e.g., plasma, serum, saliva, urine, hair), and the unit of measurement.

appropriate interventions. It is important to note that many AL biomarkers like cortisol, brain-derived neurotrophic factor, and cytokines do not have established norms—which needs to be made a priority for future research. Likewise, no known critical level or established AL threshold (e.g., scores of three or higher) has been established for use in predicting specific conditions. Because the AL index is an objective reflection of global biological functioning that is intricately interconnected with genetic, neurological, developmental, behavioral, cognitive, and social factors, AL is capturing complex interactions that cannot be fully understood until further clinical research is able to delineate specific disease trajectories. As a preliminary step, we propose that data collected in clinical practice be compiled and explored in relation to AL.

Future knowledge of underlying molecular mechanisms could provide insight into the pathophysiology of allostatic processes and perhaps help identify new promising targets for pharmacotherapy in SMI with fewer or less severe side effects. Repeated measures of an AL index before, after, and at follow-up of psychotherapy or pharmacotherapy could be a manner of comprehensively assessing treatment effects during clinical trials. For instance, the efficacy of cognitive-behavioral programs in conjunction with novel pharmacotherapy among comparison groups could be assessed with AL biomarkers that are often routinely measured in standard blood work. By applying patient-centered approaches, medical practitioners can help patients modify the antecedents of AL and PAL while respecting patients' unique strengths and weaknesses.

TREATMENT, REHABILITATION, AND PREVENTION

While schizophrenia and bipolar disorder remain extremely disabling, their prognoses have improved substantially over the past decade, in large part due to progress made in psychiatry and neuroscience. Trends in future treatment and rehabilitation will likely emphasize personalization—or individualization—so that a person's genetic background, history of stress, and personal and social resources are all taken into account. It is important to underline that early initiation of antipsychotic therapy and long-term maintenance of drug therapy are associated with better outcomes.[189] For instance, psychopharmacological interventions can exert prophylactic effects ("advance guard")[190–192] that further contribute to recovery by improving coping mechanisms and reducing distress.[193] But how can such strategies be reconciled with PAL? It is our belief that a greater understanding of allostatic processes can guide the development of more precise pharmacological approaches that should be complemented by nonmedicinal approaches. Overall, whatever the therapeutic

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strategy, the ultimate goals must focus on preventing or minimizing both the symptoms of the disease and the accumulation of AL, with subsequent comorbidities.

The growing influence of individual-centered approaches and self-management programs empowers patients to function as autonomously as possible and to focus on positive aspects of health by utilizing adaptive reserves such as social support and knowledge. Consequently, patients are encouraged to be partners in managing their disease. The utility of this paradigm shift is supported by several reports of improved health in schizophrenic patients who have undergone single nutritional and healthy lifestyle education programs,[194] weight management programs combining exercise with nutritional and motivational counseling,[195] dietary incorporation of omega-3 fatty acids,[95] and smoking cessation programs.[196] Animal research studies have revealed that food restriction regimens enhance cortical plasticity[197] and that exercise stimulates mitochondrial biogenesis and expression of neurotrophic factors,[198,199] which might have beneficial applications vis-à-vis human dietary regimens.

Encouragingly, many SMI patients are ready to initiate lifestyle changes.[200] The development of vocational and occupational rehabilitation techniques also shows promise in promoting functional improvements.[201] In addressing nonadherence to medications in patients with SMI, several experimental approaches have been developed and applied, and have improved treatment compliance.[202] Several case-management models have also succeeded in reducing the risk of readmission in populations with high hospitalization use.[203] Pharmacological interventions may help in preventing outcomes secondary to AL; for example, topiramate has been used to reduce rates of obesity among patients with SMI.[204,205]

Preventive programs are especially important. For instance, the results of an experimental environmental enrichment program revealed that intervention at the age of three to five years in an at-risk population reduced schizotypal personality scores and antisocial behavior in early adulthood.[206] Furthermore, recent advances in our understanding of neurological plasticity and reparative potential give hope for the development of suitable therapeutic interventions.[207] Even among chronic schizophrenic patients, cognitive training can induce significant increases in serum levels of brain-derived neurotrophic factor.[208] Scientist-practitioners who are focused on prevention will therefore benefit from integrating biological measures into their analytical frameworks for conceptualizing, designing, and evaluating interventions for patients with SMI.[209] AL indices could also be helpful in assessing the efficacy of treatment, rehabilitation, and prevention of core and comorbid symptoms. We believe that applying repeated measures of AL indices before and after such interventions could help ascertain their potential to promote positive changes in patients' lives that protect against the development of comorbidities.

CONCLUSION AND FUTURE DIRECTIONS

Studies are critically needed in populations with SMI (including patients with schizophrenia or bipolar disorder as well as other diseases) that assess AL in research and in clinical settings. Indeed, we know of no study that has examined the AL index in schizophrenia or in bipolar disorder even though both conditions are chronic stressors. We have provided a simple formula to calculate a clinical AL index that could be used in both laboratories and clinics to monitor physiological dysregulations, comorbidities, and treatment efficacy. AL indices could be a powerful screening tool for identifying patients at high risk of developing comorbidities. Moreover, the AL index could be used to assess long-term side effects of pharmacological treatment and complex intervention programs; no tool is currently available for that purpose.

Given the considerable health care burden associated with SMIs, interventions likely to improve the prognosis, minimize the rate of comorbidities, and promote patients' quality of life are a social priority. Within the current paradigm surrounding SMI, the research priorities, nosological classifications, treatment strategies, and social policies are all illness centered. As useful as this approach is in identifying biomolecular correlates and vulnerability factors for SMI, these elements are often not incorporated into patient-centered approaches insofar as they focus exclusively on pathology. The most significant shortcoming of this pathology-driven approach is that it ignores the immense potential to promote protective factors like personal and social resources that have been extensively reported in the empirical AL literature.[6] The concept of top-down regulation of cognitive, autonomic, and neuroendocrine function central to the AL model provides a strong rationale to support emerging trends, including in the public policy domain, that reorient therapeutic strategies and emphasize the role of healthy lifestyle promotion and social support.[210] Basing interventions on a partnership—rather than the model in which the patient is a passive consumer of health care—will further encourage patients' coping abilities and dignity.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES

1. Brundtland GH. From the World Health Organization. Mental health: new understanding, new hope. JAMA 2001; 286:2391.
2. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness: position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry 2009;24: 412–24.

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3. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 2007;64:1123–31.
4. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 2002;68:167–81.
5. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation—allostatic load and its health consequences. MacArthur studies of successful aging. Arch Intern Med 1997;157:2259–68.
6. Beckie TM. A systematic review of allostatic load, health, and health disparities. Biol Res Nurs 2012;14:311–46.
7. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev 2010;35:2–16.
8. Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev 2008;32:675–92.
9. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J, eds. Handbook of life stress, cognition and health. New York: Wiley, 1988:629–49.
10. Sterling P. Principles of allostasis: optimal design, predictive regulation, pathophysiology and rational therapeutics. In: Schulkin J, ed. Allostasis, homeostasis, and the costs of adaptation. Cambridge: Cambridge University Press, 2004:17–64.
11. Schulkin J. Allostasis: a neural behavioral perspective. Horm Behav 2003;43:21–7; discussion 8–30.
12. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000;21:55–89.
13. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 1998;840:33–44.
14. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
15. McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 2000;22:108–24.
16. Juster RP, Lupien SJ. Chronic stress and allostatic load. In: Schenck-Gustafsson K, DeCola PR, Pfaff DW, Pisetsky DS, eds. Handbook of clinical gender medicine. Basel: Karger, 2012:70–81.
17. Seeman E, Singer BH, Rowe J, Horwitz RI, McEwen B. Price of adaptation—allostatic load and its health consequences. Arch Intern Med 1997;157:2259–68.
18. Gruenewald TL, Mroczek DK, Ryff CD, Singer BH. Diverse pathways to positive and negative affect in adulthood and later life: an integrative approach using recursive partitioning. Dev Psychol 2008;44:330–43.
19. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci U S A 2001;98:4770–5.
20. Goldman N, Turra CM, Glei DA, Lin YH, Weinstein M. Physiological dysregulation and changes in health in an older population. Exp Gerontol 2006;41:862–70.
21. Goldman N, Turra CM, Glei DA, Seplaki CL, Lin YH, Weinstein M. Predicting mortality from clinical and nonclinical biomarkers. J Gerontol A Biol Sci Med Sci 2006;61:1070–4.
22. Seplaki CL, Goldman N, Glei D, Weinstein M. A comparative analysis of measurement approaches for physiological dysregulation in an older population. Exp Gerontol 2005;40:438–49.
23. Seplaki CL, Goldman N, Weinstein M, Lin YH. How are biomarkers related to physical and mental well-being? J Gerentol 2004;59A:201–17.
24. Seplaki CL, Goldman N, Weinstein M, Lin YH. Measurement of cumulative physiological dysregulation in an older population. Demography 2006;43:165–83.
25. Karlamangla AS, Singer BH, Seeman TE. Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur studies of successful aging. Psychosom Med 2006;68:500–7.
26. Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, et al. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. J Clin Psychiatry 2008;69:514–9.
27. Brown S. Excess mortality of schizophrenia: a meta-analysis. Br J Psychiatry 1997;171:502–8.
28. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. J Clin Psychiatry 2006;67 suppl 9:25–30; discussion 36–42.
29. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. BMJ 2000;321:483–4.
30. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J 2005;150:1115–21.
31. Holt RI, Bushe C, Citrome L. Diabetes and schizophrenia 2005: are we any closer to understanding the link? J Psychopharmacol 2005;19:56–65.
32. McIntyre RS, Konarski JZ, Misener VL, Kennedy SH. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. Ann Clin Psychiatry 2005;17:83–93.
33. McEwen BS. Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. Metabolism 2003;52:10–6.
34. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.
35. Muck-Seler D, Pivac N, Mustapic M, Crncevic Z, Jakovljevic M, Sagud M. Platelet serotonin and plasma prolactin and cortisol in healthy, depressed and schizophrenic women. Psychiatry Res 2004;127:217–26.
36. Walsh P, Spelman L, Sharifi N, Thakore JH. Male patients with paranoid schizophrenia have greater ACTH and cortisol secretion in response to metoclopramide-induced AVP release. Psychoneuroendocrinology 2005;30:431–7.
37. Gallagher P, Watson S, Smith MS, Young AH, Ferrier IN. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. Schizophr Res 2007;90:258–65.
38. Ritsner M, Gibel A, Maayan R, et al. State and trait related predictors of serum cortisol to DHEA(S) molar ratios and hormone concentrations in schizophrenia patients. Eur Neuropsychopharmacol 2007;17:257–64.
39. Yilmaz N, Herken H, Cicek HK, Celik A, Yurekli M, Akyol O. Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. Med Princ Pract 2007;16:137–41.
40. Linkowski P, Kerkhofs M, Van Onderbergen A, et al. The 24-hour profiles of cortisol, prolactin, and growth hormone secretion in mania. Arch Gen Psychiatry 1994;51:616–24.
41. Muck-Seler D, Pivac N, Jakovljevic M, Brzovic Z. Platelet serotonin, plasma cortisol, and dexamethasone suppression test in schizophrenic patients. Biol Psychiatry 1999;45:1433–9.
42. Ismail K, Murray RM, Wheeler MJ, O'Keane V. The dexamethasone suppression test in schizophrenia. Psychol Med 1998;28:311–7.
43. Sher L. Combined dexamethasone suppression-corticotropin-releasing hormone stimulation test in studies of depression, alcoholism, and suicidal behavior. ScientificWorldJournal 2006;6:1398–404.

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44. Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. Br J Psychiatry 2004;184:496–502.
45. Vieta E, Gasto C, Martinez de Osaba MJ, et al. Prediction of depressive relapse in remitted bipolar patients using corticotrophin-releasing hormone challenge test. Acta Psychiatr Scand 1997;95:205–11.
46. Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol 2009;30:65–91.
47. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008;63: 801–8.
48. Breunis MN, Kupka RW, Nolen WA, et al. High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder. Biol Psychiatry 2003;53:157–65.
49. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord 2007;104:91–5.
50. Liu HC, Yang YY, Chou YM, Chen KP, Shen WW, Leu SJ. Immunologic variables in acute mania of bipolar disorder. J Neuroimmunol 2004;150:116–22.
51. O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. J Affect Disord 2006;90:263–7.
52. Ortiz-Dominguez A, Hernandez ME, Berlanga C, et al. Immune variations in bipolar disorder: phasic differences. Bipolar Disord 2007;9:596–602.
53. Tsai SY, Chen KP, Yang YY, et al. Activation of indices of cell-mediated immunity in bipolar mania. Biol Psychiatry 1999;45:989–94.
54. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 2004;92: 347–55.
55. Bob P, Raboch J, Maes M, et al. Depression, traumatic stress and interleukin-6. J Affect Disord 2010;120:231–4.
56. Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord 2009;11:657–62.
57. Fleet-Michaliszyn SB, Soreca I, Otto AD, et al. A prospective observational study of obesity, body composition, and insulin resistance in 18 women with bipolar disorder and 17 matched control subjects. J Clin Psychiatry 2008;69:1892–900.
58. Fagiolini A, Frank E, Turkin S, Houck PR, Soreca I, Kupfer DJ. Metabolic syndrome in patients with bipolar disorder. J Clin Psychiatry 2008;69:678–9.
59. Trushina E, McMurray CT. Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases. Neuroscience 2007; 145:1233–48.
60. Juster RP, Bizik G, Picard M, et al. A transdisciplinary perspective of chronic stress in relation to psychopathology throughout life span development. Dev Psychopathol 2011; 23:725–76.
61. Anisman H, Hayley S. Illness comorbidity as a biomarker? J Psychiatry Neurosci 2012;37:221–3.
62. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull 2009;35: 383–402.
63. Krishnan KR. Psychiatric and medical comorbidities of bipolar disorder. Psychosom Med 2005;67:1–8.
64. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001; 158:420–6.
65. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990; 264:2511–8.
66. George O, Le Moal M, Koob GF. Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. Physiol Behav 2012;106:58–64.
67. Koob GF. Alcoholism: allostasis and beyond. Alcohol Clin Exp Res 2003;27:232–43.
68. Koob GF, Ahmed SH, Boutrel B, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev 2004;27:739–49.
69. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 2001;24: 97–129.
70. Schulkin J. Addiction to drugs: allostatic regulation under duress. In: Rethinking homestasis: allostatic regulation in physiology and pathophysiology. Cambridge, MA: MIT, 2003:131–60.
71. Valdez GR, Koob GF. Allostasis and dysregulation of corticotropin-releasing factor and neuropeptide Y systems: implications for the development of alcoholism. Pharmacol Biochem Behav 2004;79:671–89.
72. Grande I, Magalhaes PV, Kunz M, Vieta E, Kapczinski F. Mediators of allostasis and systemic toxicity in bipolar disorder. Physiol Behav 2012;106:46–50.
73. McEwen BS. Mood disorders and allostatic load. Biol Psychiatry 2003;54:200–7.
74. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 2005;54:20–3.
75. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 2004;1032:1–7.
76. Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 1998;23: 219–43.
77. Schulkin J, McEwen BS, Gold PW. Allostasis, amygdala, and anticipatory angst. Neurosci Biobehav Rev 1994;18:385–96.
78. McEwen BS. The neurobiology and neuroendocrinology of stress. Implications for post-traumatic stress disorder from a basic science perspective. Psychiatr Clin North Am 2002;25: 469–94, ix.
79. Birmaher B, Kennah A, Brent D, Ehmann M, Bridge J, Axelson D. Is bipolar disorder specifically associated with panic disorder in youths? J Clin Psychiatry 2002;63:414–9.
80. MacQueen GM, Marriott M, Begin H, Robb J, Joffe RT, Young LT. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. Bipolar Disord 2003;5:349–55.
81. Elman I, Borsook D, Lukas SE. Food intake and reward mechanisms in patients with schizophrenia: implications for metabolic disturbances and treatment with second-generation antipsychotic agents. Neuropsychopharmacology 2006;31: 2091–120.
82. Dallman MF, Pecoraro N, Akana SF, et al. Chronic stress and obesity: a new view of "comfort food." Proc Natl Acad Sci U S A 2003;100:11696–701.
83. Vieta E, Popovic D, Rosa AR, et al. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur Psychiatry 2013; 28:21–9.
84. Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. Neuropsychopharmacology 2008;33:2217–27.

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85. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. Curr Pharm Des 2009;15:2550–9.
86. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003;160:13–23.
87. Kapur S, Agid O, Mizrahi R, Li M. How antipsychotics work—from receptors to reality. NeuroRx 2006;3:10–21.
88. Paradiso S, Andreasen NC, Crespo-Facorro B, et al. Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. Am J Psychiatry 2003; 160:1775–83.
89. Gur RE, McGrath C, Chan RM, et al. An fMRI study of facial emotion processing in patients with schizophrenia. Am J Psychiatry 2002;159:1992–9.
90. Sturm R. The effects of obesity, smoking, and drinking on medical problems and costs. Health Aff (Millwood) 2002; 21:245–53.
91. Lopresti AL, Drummond PD. Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. Prog Neuropsychopharmacol Biol Psychiatry 2013;45:92–9.
92. Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. Psychol Med 1999;29: 697–701.
93. Strassnig M, Brar JS, Ganguli R. Nutritional assessment of patients with schizophrenia: a preliminary study. Schizophr Bull 2003;29:393–7.
94. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. Br J Psychiatry 2003;183:534–9.
95. Peet M. Diet, diabetes and schizophrenia: review and hypothesis. Br J Psychiatry Suppl 2004;47:S102–5.
96. Anderson EJ, Lustig ME, Boyle KE, et al. Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. J Clin Invest 2009;119:573–81.
97. Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu Rev Genet 2005;39:359–407.
98. Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol Psychiatry 2001;50:71–83.
99. Krystal JH, D'Souza DC, Gallinat J, et al. The vulnerability to alcohol and substance abuse in individuals diagnosed with schizophrenia. Neurotox Res 2006;10:235–52.
100. Fagen ZM, Mitchum R, Vezina P, McGehee DS. Enhanced nicotinic receptor function and drug abuse vulnerability. J Neurosci 2007;27:8771–8.
101. De Hert M, Schreurs V, Vancampfort D, van Winkel R. Metabolic syndrome in people with schizophrenia: a review. World Psychiatry 2009;8:15–22.
102. Mueser KT, Bellack AS, Blanchard JJ. Comorbidity of schizophrenia and substance abuse: implications for treatment. J Consult Clin Psychol 1992;60:845–56.
103. Mobascher A, Winterer G. The molecular and cellular neurobiology of nicotine abuse in schizophrenia. Pharmacopsychiatry 2008;41 suppl 1:S51–9.
104. Freedman R, Hall M, Adler LE, Leonard S. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 1995;38:22–33.
105. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology (Berl) 2006;184:523–39.
106. Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993;150:1856–61.
107. Harris JG, Kongs S, Allensworth D, et al. Effects of nicotine on cognitive deficits in schizophrenia. Neuropsychopharmacology 2004;29:1378–85.
108. Myers CS, Robles O, Kakoyannis AN, et al. Nicotine improves delayed recognition in schizophrenic patients. Psychopharmacology (Berl) 2004;174:334–40.
109. de Leon J, Dadvand M, Canuso C, White AO, Stanilla JK, Simpson GM. Schizophrenia and smoking: an epidemiological survey in a state hospital. Am J Psychiatry 1995;152: 453–5.
110. Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. Nature 1997;390:401–4.
111. Cardenas L, Tremblay LK, Naranjo CA, Herrmann N, Zack M, Busto UE. Brain reward system activity in major depression and comorbid nicotine dependence. J Pharmacol Exp Ther 2002;302:1265–71.
112. Goswami S, Mattoo SK, Basu D, Singh G. Substance-abusing schizophrenics: do they self-medicate? Am J Addict 2004;13: 139–50.
113. Juckel G, Sass L, Heinz A. Anhedonia, self-experience in schizophrenia, and implications for treatment. Pharmacopsychiatry 2003;36 suppl 3:S176–80.
114. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet 1999;36:425–38.
115. Zaslove MO, Russell RL, Ross E. Effect of caffeine intake on psychotic in-patients. Br J Psychiatry 1991;159:565–7.
116. Hughes JR, McHugh P, Holtzman S. Caffeine and schizophrenia. Psychiatr Serv 1998;49:1415–7.
117. de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. Psychiatr Serv 2004;55:491–3.
118. Haskell CF, Kennedy DO, Wesnes KA, Scholey AB. Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. Psychopharmacology (Berl) 2005;179:813–25.
119. Tanda G, Goldberg SR. Alteration of the behavioral effects of nicotine by chronic caffeine exposure. Pharmacol Biochem Behav 2000;66:47–64.
120. Adolfo AB, AhnAllen CG, Tidey JW. Effects of smoking cues on caffeine urges in heavy smokers and caffeine consumers with and without schizophrenia. Schizophr Res 2009;107:192–7.
121. Nasrallah HA, Meyer JM, Goff DC, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophr Res 2006;86:15–22.
122. De Hert M, Falissard B, Mauri M, Shaw K, Wetterling T. Epidemiological study for the evaluation of metabolic disorders in patients with schizophrenia: the METEOR Study. Eur Neuropsychopharmacol 2008;18(suppl 4):S444.
123. Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. Arch Gen Psychiatry 2009;66:713–20.
124. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical comorbidity in schizophrenia. Schizophr Bull 1996;22: 413–30.
125. Lublin H, Eberhard J, Levander S. Current therapy issues and unmet clinical needs in the treatment of schizophrenia: a review of the new generation antipsychotics. Int Clin Psychopharmacol 2005;20:183–98.

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126. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics : differential risk and clinical implications. CNS Drugs 2007;21:911–36.
127. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003;28:519–26.
128. Muller DJ, Muglia P, Fortune T, Kennedy JL. Pharmacogenetics of antipsychotic-induced weight gain. Pharmacol Res 2004;49:309–29.
129. Ellingrod VL, Perry PJ, Ringold JC, et al. Weight gain associated with the -759C/T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet 2005;134B:76–8.
130. Picard M, Turnbull DM. Linking the metabolic state and mitochondrial DNA in chronic disease, health and aging. Diabetes 2013 (forthcoming).
131. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature 2008; 454:463–9.
132. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 1999;282: 1547–53.
133. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004;351: 2694–703.
134. Gustafson D. A life course of adiposity and dementia. Eur J Pharmacol 2008;585:163–75.
135. Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab 2012;16:706–22.
136. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005;19 suppl 1:1–93.
137. Saari K, Koponen H, Laitinen J, et al. Hyperlipidemia in persons using antipsychotic medication: a general population-based birth cohort study. J Clin Psychiatry 2004;65:547–50.
138. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs 2004;64:701–23.
139. Vendsborg PB, Bech P, Rafaelsen OJ. Lithium treatment and weight gain. Acta Psychiatr Scand 1976;53:139–47.
140. Swann AC. Major system toxicities and side effects of anticonvulsants. J Clin Psychiatry 2001;62 suppl 14:16–21.
141. Manderbacka K, Sund R, Koski S, Keskimaki I, Elovainio M. Diabetes and depression? Secular trends in the use of antidepressants among persons with diabetes in Finland in 1997–2007. Pharmacoepidemiol Drug Saf 2011;20:338–43.
142. Awad AG. Subjective tolerability of antipsychotic medications and the emerging science of subjective tolerability disorders. Expert Rev Pharmacoecon Outcomes Res 2010;10:1–4.
143. Voruganti LP, Awad AG. Is neuroleptic dysphoria a variant of drug-induced extrapyramidal side effects? Can J Psychiatry 2004;49:285–9.
144. Tandon R. Safety and tolerability: how do newer generation "atypical" antipsychotics compare? Psychiatr Q 2002;73: 297–311.
145. Mizrahi R, Rusjan P, Agid O, et al. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. Am J Psychiatry 2007;164:630–7.
146. Voruganti LNP, Awad AG. Role of dopamine in pleasure, reward and subjective responses to drugs. The neuropsychopharmacology of quality of life in schizophrenia. In: Ritsner MS, Awad AG, eds. Quality of life impairment in schizophrenia, mood and anxiety disorders. Dordrecht: Springer, 2007.
147. de Haan L, van Bruggen M, Lavalaye J, Booij J, Dingemans PM, Linszen D. Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am J Psychiatry 2003;160:303–9.
148. Kapur S, Remington G, Jones C, et al. High levels of dopamine D2 receptor occupancy with low-dose haloperidol treatment: a PET study. Am J Psychiatry 1996;153:948–50.
149. Nordstrom AL, Farde L, Wiesel FA, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatry 1993;33:227–35.
150. Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. J Psychiatry Neurosci 2000;25:161–6.
151. Voruganti LN, Heslegrave RJ, Awad AG. Neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. J Nerv Ment Dis 1997;185:463–5.
152. Noordsy DL, Green AI. Pharmacotherapy for schizophrenia and co-occurring substance use disorders. Curr Psychiatry Rep 2003;5:340–6.
153. Kosten TA, Nestler EJ. Clozapine attenuates cocaine conditioned place preference. Life Sci 1994;55:PL9–14.
154. Voruganti LN, Slomka P, Zabel P, Mattar A, Awad AG. Cannabis induced dopamine release: an in-vivo SPECT study. Psychiatry Res 2001;107:173–7.
155. Breier A, Su TP, Saunders R, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A 1997;94:2569–74.
156. Laruelle M, Abi-Dargham A, van Dyck CH, et al. SPECT imaging of striatal dopamine release after amphetamine challenge. J Nucl Med 1995;36:1182–90.
157. Schlaepfer TE, Pearlson GD, Wong DF, Marenco S, Dannals RF. PET study of competition between intravenous cocaine and [11C]raclopride at dopamine receptors in human subjects. Am J Psychiatry 1997;154:1209–13.
158. D'Souza DC, Abi-Saab WM, Madonick S, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry 2005; 57:594–608.
159. Munro CA, McCaul ME, Oswald LM, et al. Striatal dopamine release and family history of alcoholism. Alcohol Clin Exp Res 2006;30:1143–51.
160. Oswald LM, Wong DF, McCaul M, et al. Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. Neuropsychopharmacology 2005;30:821–32.
161. Peretti CS, Danion JM, Kauffmann-Muller F, Grange D, Patat A, Rosenzweig P. Effects of haloperidol and amisulpride on motor and cognitive skill learning in healthy volunteers. Psychopharmacology (Berl) 1997;131:329–38.
162. Saeedi H, Remington G, Christensen BK. Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. Schizophr Res 2006;85:222–31.
163. Kim SH, Han DH, Joo SY, Min KJ. The effect of dopamine partial agonists on the nicotine dependency in patients with schizophrenia. Hum Psychopharmacol 2010;25:187–90.
164. de Haan L, Booij J, Lavalaye J, van Amelsvoort T, Linszen D. Occupancy of dopamine D2 receptors by antipsychotic drugs is related to nicotine addiction in young patients with schizophrenia. Psychopharmacology (Berl) 2006;183:500–5.

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165. McEvoy J, Freudenreich O, McGee M, VanderZwaag C, Levin E, Rose J. Clozapine decreases smoking in patients with chronic schizophrenia. Biol Psychiatry 1995;37:550–2.
166. Li S, Kim KY, Kim JH, Park MS, Bahk JY, Kim MO. Chronic nicotine and smoking treatment increases dopamine transporter mRNA expression in the rat midbrain. Neurosci Lett 2004;363:29–32.
167. Drew AE, Werling LL. Nicotinic receptor-mediated regulation of the dopamine transporter in rat prefrontocortical slices following chronic in vivo administration of nicotine. Schizophr Res 2003;65:47–55.
168. Yang YK, Nelson L, Kamaraju L, Wilson W, McEvoy JP. Nicotine decreases bradykinesia-rigidity in haloperidol-treated patients with schizophrenia. Neuropsychopharmacology 2002;27:684–6.
169. Anfang MK, Pope HG Jr. Treatment of neuroleptic-induced akathisia with nicotine patches. Psychopharmacology (Berl) 1997;134:153–6.
170. Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. Am J Psychiatry 1992;149:1189–94.
171. Silvestri S, Negrete JC, Seeman MV, Shammi CM, Seeman P. Does nicotine affect D2 receptor upregulation? A case-control study. Acta Psychiatr Scand 2004;109:313–7; discussion 7–8.
172. Seeman P. Tardive dyskinesia, dopamine receptors, and neuroleptic damage to cell membranes. J Clin Psychopharmacol 1988;8:3S–9S.
173. Minzenberg MJ, Poole JH, Benton C, Vinogradov S. Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. Am J Psychiatry 2004;161:116–24.
174. Vinogradov S, Fisher M, Warm H, Holland C, Kirshner MA, Pollock BG. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. Am J Psychiatry 2009;166:1055–62.
175. Levin ED, Wilson W, Rose JE, McEvoy J. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 1996;15:429–36.
176. Strand JE, Nyback H. Tobacco use in schizophrenia: a study of cotinine concentrations in the saliva of patients and controls. Eur Psychiatry 2005;20:50–4.
177. de Leon J, Diaz FJ, Aguilar MC, Jurado D, Gurpegui M. Does smoking reduce akathisia? Testing a narrow version of the self-medication hypothesis. Schizophr Res 2006;86:256–68.
178. Lorberg B, Wilens TE, Martelon M, Wong P, Parcell T. Reasons for substance use among adolescents with bipolar disorder. Am J Addict 2010;19:474–80.
179. Schreiber S, Backer MM, Weizman R, Pick CG. Augmentation of opioid induced antinociception by the atypical antipsychotic drug risperidone in mice. Neurosci Lett 1997;228:25–8.
180. Schreiber S, Getslev V, Backer MM, Weizman R, Pick CG. The atypical neuroleptics clozapine and olanzapine differ regarding their antinociceptive mechanisms and potency. Pharmacol Biochem Behav 1999;64:75–80.
181. Weizman T, Pick CG, Backer MM, Rigai T, Bloch M, Schreiber S. The antinociceptive effect of amisulpride in mice is mediated through opioid mechanisms. Eur J Pharmacol 2003;478:155–9.
182. Fe-Bornstein M, Watt SD, Gitlin MC. Improvement in the level of psychosocial functioning in chronic pain patients with the use of risperidone. Pain Med 2002;3:128–31.
183. Kiser RS, Cohen HM, Freedenfeld RN, Jewell C, Fuchs PN. Olanzapine for the treatment of fibromyalgia symptoms. J Pain Symptom Manage 2001;22:704–8.
184. Silberstein SD, Peres MF, Hopkins MM, Shechter AL, Young WB, Rozen TD. Olanzapine in the treatment of refractory migraine and chronic daily headache. Headache 2002;42:515–8.
185. Marchesi GF, Santone G, Cotani P, Giordano A, Chelli F. The therapeutic role of naltrexone in negative symptom schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:1239–49.
186. Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. Physiol Behav 2002;76:365–77.
187. Will MJ, Franzblau EB, Kelley AE. Nucleus accumbens mu-opioids regulate intake of a high-fat diet via activation of a distributed brain network. J Neurosci 2003;23:2882–8.
188. Petrakis IL, O'Malley S, Rounsaville B, Poling J, McHugh-Strong C, Krystal JH. Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. Psychopharmacology (Berl) 2004;172:291–7.
189. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56:241–7.
190. Haroun N, Dunn L, Haroun A, Cadenhead KS. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. Schizophr Bull 2006;32:166–78.
191. McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry 2006;163:790–9.
192. Miller TJ, Zipursky RB, Perkins D, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the "prodromal" sample. Schizophr Res 2003;61:19–30.
193. Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. Schizophr Bull 2008;34:523–37.
194. Wirshing DA, Smith RA, Erickson ZD, Mena SJ, Wirshing WC. A wellness class for inpatients with psychotic disorders. J Psychiatr Pract 2006;12:24–9.
195. Wreeland B, Minski S, Menza M, Radler DR, Roemheld-Hamm B, Stern R. A program for managing weight gain associated with atypical antipsychotics. Psychiatr Serv 2003;54:1155–7.
196. Robson D, Gray R. Serious mental illness and physical health problems: a discussion paper. Int J Nurs Stud 2007;44:457–66.
197. Spolidoro M, Baroncelli L, Putignano E, Maya-Vetencourt JF, Viegi A, Maffei L. Food restriction enhances visual cortex plasticity in adulthood. Nat Commun 2011;2:320.
198. Seifert T, Brassard P, Wissenberg M, et al. Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol 2010;298:R372–7.
199. Steiner JL, Murphy EA, McClellan JL, Carmichael MD, Davis JM. Exercise training increases mitochondrial biogenesis in the brain. J Appl Physiol 2011;111:1066–71.
200. Archie SM, Goldberg JO, Akhtar-Danesh N, Landeen J, McColl L, McNiven J. Psychotic disorders, eating habits, and physical activity: who is ready for lifestyle changes? Psychiatr Serv 2007;58:233–9.
201. Twamley EW, Jeste DV, Lehman AF. Vocational rehabilitation in schizophrenia and other psychotic disorders: a literature

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review and meta-analysis of randomized controlled trials. J Nerv Ment Dis 2003;191:515–23.
202. Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment non-adherence in psychosis: meta-analysis. Br J Psychiatry 2003;183:197–206.
203. Burns T, Catty J, Dash M, Roberts C, Lockwood A, Marshall M. Use of intensive case management to reduce time in hospital in people with severe mental illness: systematic review and meta-regression. BMJ 2007;335:336.
204. Afshar H, Roohafza H, Mousavi G, et al. Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. J Psychopharmacol 2009;23:157–62.
205. Levy E, Agbokou C, Ferreri F, Chouinard G, Margolese HC. Topiramate-induced weight loss in schizophrenia: a retrospective case series study. Can J Clin Pharmacol 2007;14:e234–9.
206. Raine A, Mellingen K, Liu J, Venables P, Mednick SA. Effects of environmental enrichment at ages 3–5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. Am J Psychiatry 2003;160:1627–35.
207. Kandel ER. Biology and the future of psychoanalysis: a new intellectual framework for psychiatry revisited. Am J Psychiatry 1999;156:505–24.
208. Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon SH. Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? Biol Psychiatry 2009;66:549–53.
209. Cicchetti D, Gunnar MR. Integrating biological measures into the design and evaluation of preventive interventions. Dev Psychopathol 2008;20:737–43.
210. McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol 2008;583:174–85.

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