



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

Gustav Bizik, MD, Martin Picard, PhD, Rami Nijjar, MSc, Valérie Tourjman, MD, Bruce S. McEwen, PhD, Sonia J. Lupien, PhD, and Robert-Paul Juster, MSc

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 indices⁵ 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 colleagues⁸ 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

From the Department of Psychiatry and Center for Neuropsychiatric Research of Traumatic Stress, Charles University, Czech Republic (Dr. Bizik); University of Pennsylvania and Center for Mitochondrial and Epigenomic Medicine, Children’s Hospital of Philadelphia, Philadelphia (Dr. Picard); Department of Psychology and Center for Research in Human Development, Concordia University, Canada (Ms. Nijjar); Department of Psychiatry (Drs. Tourjman and Lupien), Fernand-Seguin Research Centre at Louis-H. Lafontaine Hospital (Drs. Tourjman and Lupien, and Mr. Juster), and Center for Studies on Human Stress (Dr. Lupien and Mr. Juster), University of Montreal; Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, Rockefeller University (Dr. McEwen); Department of Neurology and Neurosurgery, McGill University (Mr. Juster).

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Correspondence: Robert-Paul Juster, 7401 Hochelaga, Louis Riel Pavillon, Unit 226, Room RI-2678, Montreal, Quebec, Canada, H1N 3M5. Email: robert.juster@mail.mcgill.ca

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Table 1
Prevalence of Comorbidities Among Medicated Schizophrenic and Bipolar Patients

Condition	Comorbidity	Estimated prevalence of comorbidity (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 Eyer⁹ 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 Eyer⁹ 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

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 Eyer⁹ 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 index⁵ 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 thresholds⁵ 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- α) exerts *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

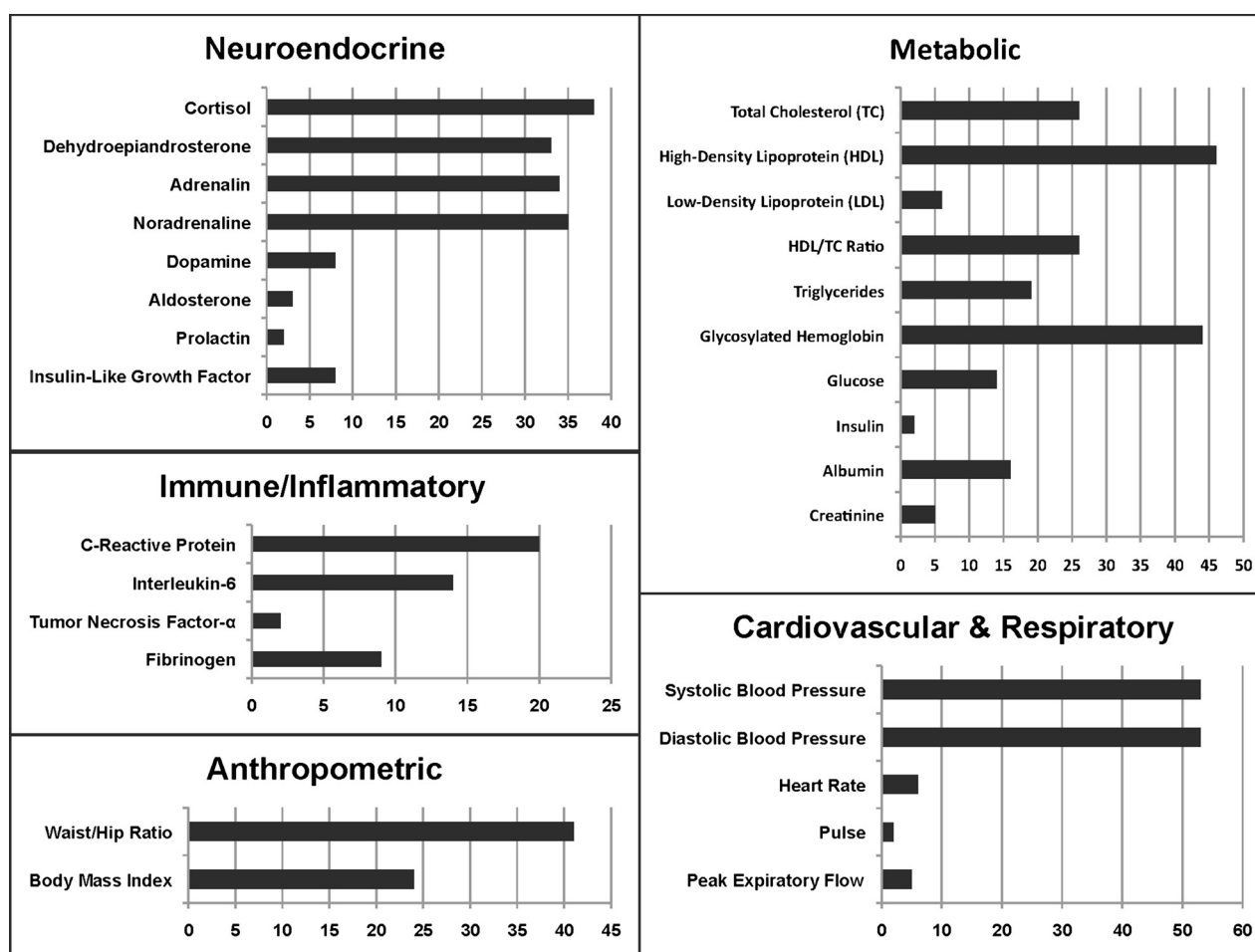


Figure 1. Frequency of studies using specific biomarkers of allostatic load as incorporated into allostatic load algorithms (based on approximately 60 reports).^{7,16}

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, pathophysiological 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 patients⁶⁵ and 60% of bipolar patients⁶³ 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

Table 3		
Physiological Dysregulations in Allostatic Load Mediators in Schizophrenia and Bipolar Disorder		
Biomarker	Schizophrenia	Bipolar disorder
Cortisol (basal peripheral levels)	Drug-naïve 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 disorder⁷⁹ 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-α. ^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.			

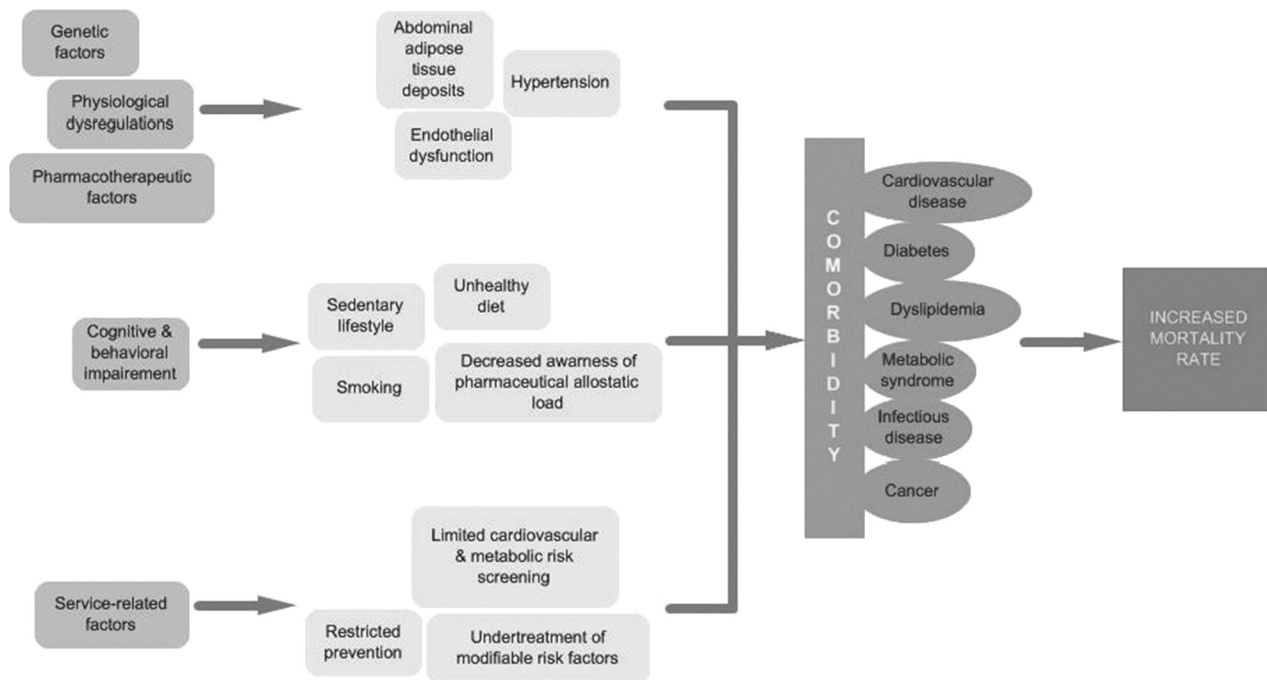


Figure 2. Pathways to comorbidity and mortality in schizophrenia and bipolar disorder. Central to every domain depicted are the direct and indirect effects of chronic stress and concomitant mediators of allostatic load.

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 schizophrenia⁸¹ 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 fat⁹² 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

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 α -7 subunit of the nicotinic acetylcholine receptor is involved in nicotine's positive effects on memory function¹⁰⁵ 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 models¹¹⁰ and contributes to the alleviation of negative affective symptoms in depressed¹¹¹ and schizophrenic^{112,113} patients. Smoking by-products 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 symptoms¹¹⁶ 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

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 carbamazepine¹⁴⁰—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 comorbidities, 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 regions¹⁴⁵ involved in

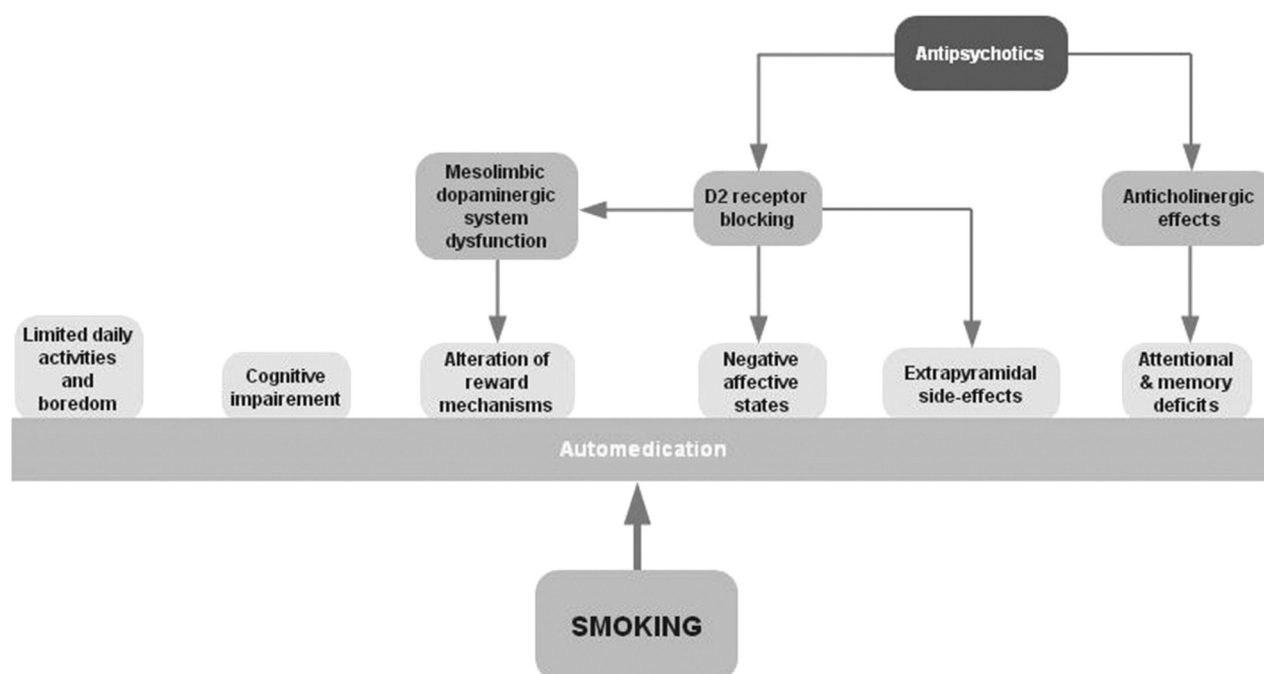


Figure 3. Smoking as an example of pharmacological allostatic load. Smoking is used to self-medicate against symptoms iatrogenically induced by prescribed antipsychotic medications.⁶⁰

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 cocaine¹⁵⁷ 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 function¹⁶¹ 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 area¹⁶⁶ 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 upregulation¹⁷¹ associated with extrapyramidal symptoms.¹⁷² A similar finding was shown in a human

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 receptors¹⁷³ 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

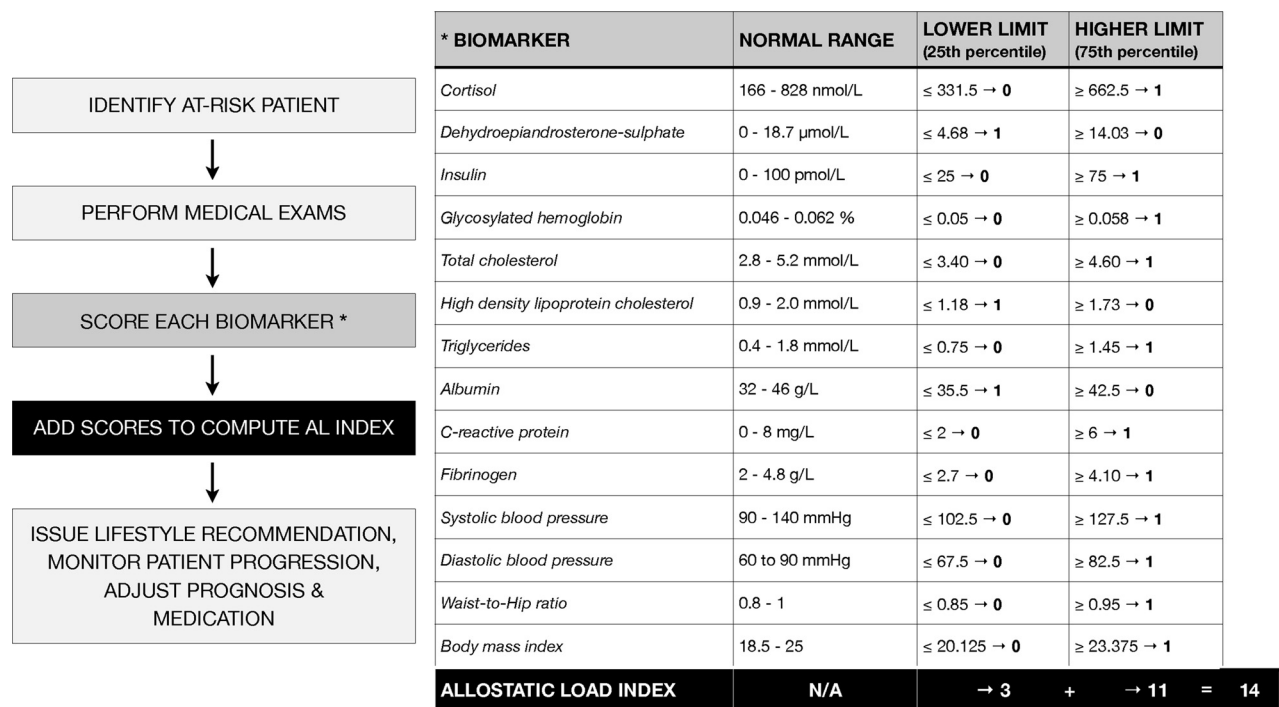


Figure 4. Clinical approach to calculating and interpreting allostatic load indices. Upon identifying patients at high risk of developing comorbidities, an allostatic load index can be easily calculated based on clinical norms for biomarkers routinely collected.^{7,16} The 14 biomarkers listed here as 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

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 plasticity¹⁹⁷ 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 non-adherence 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.

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