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Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder

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People with severe mental illness have a considerably shorter lifespan than the general population. This excess mortality is mainly due to physical illness. Next to mental illness-related factors, unhealthy lifestyle, and disparities in health care access and utilization, psychotropic medications can contribute to the risk of physical morbidity and mortality. We systematically reviewed the effects of antipsychotics, antidepressants and mood stabilizers on physical health outcomes in people with schizophrenia, depression and bipolar disorder. Updating and expanding our prior systematic review published in this journal, we searched MEDLINE (November 2009 - November 2014), combining the MeSH terms of major physical disease categories (and/or relevant diseases within these categories) with schizophrenia, major depressive disorder and bipolar disorder, and the three major psychotropic classes which received regulatory approval for these disorders, i.e., antipsychotics, antidepressants and mood stabilizers. We gave precedence to results from (systematic) reviews and meta-analyses wherever possible. Antipsychotics, and to a more restricted degree antidepressants and mood stabilizers, are associated with an increased risk for several physical diseases, including obesity, dyslipidemia, diabetes mellitus, thyroid disorders, hyponatremia; cardiovascular, respiratory tract, gastrointestinal, haematological, musculoskeletal and renal diseases, as well as movement and seizure disorders. Higher dosages, polypharmacy, and treatment of vulnerable (e.g., old or young) individuals are associated with greater absolute (elderly) and relative (youth) risk for most of these physical diseases. To what degree medication-specific and patient-specific risk factors interact, and how adverse outcomes can be minimized, allowing patients to derive maximum benefits from these medications, requires adequate clinical attention and further research.

Key words: Physical illness, cardiovascular, metabolic, endocrine, gastrointestinal, respiratory, schizophrenia, bipolar disorder, depression, antipsychotics, antidepressants, mood stabilizers

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People with severe mental illness (SMI), particularly schizophrenia, bipolar disorder and major depressive disorder, have an average mortality rate that is 2-3 times higher than the general population (1-3), corresponding to a 10-25 year shortened life expectancy (2-9). The most common causes of death in people with SMI are physical diseases (10).

Mental illness-related factors, unhealthy lifestyle choices, as well as disparities, not only in health care access and utilization, but also in health care provision, contribute to the poorer physical health outcomes in people with SMI (11). However, the use of psychotropic medications can further increase the risk of physical complications/disorders.

Thorough knowledge about the effects of frequently used psychotropic medications – antipsychotics, antidepressants and mood stabilizers – on physical health in people with SMI can inform better treatment choices and/or strategies.

Updating and expanding our prior review published in this journal (11), we systematically searched MEDLINE (November 2009 - November 2014) for epidemiological, morbidity and mortality data combining the MeSH terms of major physical disease categories and/or relevant diseases within these categories (Table 1) with schizophrenia, major depressive disorder and bipolar disorder, and the three major psychotropic classes which received regulatory approval for these psychiatric disorders, i.e., antipsychotics,

antidepressants and mood stabilizers. While psychotropic medications can potentially increase the risk of many physical diseases, we focused on a selected number of diseases. We further restricted our search to pertinent English-language (systematic) reviews and meta-analyses, although for certain physical diseases relevant individual studies were selected.

The MEDLINE searches yielded 13,477 hits (Table 1). Below, we summarize the findings concerning the relationship of antipsychotics, antidepressants and mood stabilizers to each physical illness/domain.

NUTRITIONAL AND METABOLIC DISEASES

Obesity

People with SMI are, compared to the general population, at increased risk for being overweight and obese (12-15). The likelihood of being obese is increased 2.8-4.4 fold in patients with schizophrenia and 1.2-1.7 fold in those with major depression or bipolar disorder (16-22).

Weight gain – commonly assessed as body weight change, change in body mass index, or clinically relevant ($\geq 7\%$) weight change from baseline (23,24) – is a well-established side effect of antipsychotics during the acute and maintenance

Table 1 MEDLINE search results: disease category (+SMI, + psychotropic)

Nutritional and metabolic diseases: 1,958 hits (358 reviews)

Obesity: 1,550 hits (266 reviews)

Dyslipidemia: 408 hits (92 reviews)

Endocrine system diseases: 1,709 hits (324 reviews)

Diabetes mellitus/diabetic ketoacidosis: 1,305 hits (256 reviews)

Thyroid disorders/hyponatremia/SIADH: 404 hits (68 reviews)

Cardiovascular diseases: 1,394 hits (211 reviews)

Coronary heart disease/sudden cardiac death: 617 hits (85 reviews)

Cerebrovascular disease: 777 hits (126 reviews)

Hypertension/myocarditis: 965 hits (165 reviews)

Respiratory tract diseases

Pneumonia: 108 hits (11 reviews)

Gastrointestinal diseases

Liver diseases/constipation: 672 hits (150 reviews)

Neoplasms

Cancer: 2,387 hits (396 reviews)

Musculoskeletal diseases

Osteoporosis: 163 hits (49 reviews)

Haematologic diseases: 364 hits (40 reviews)

Other diseases: 4,121 hits (890 reviews)

SMI – severe mental illness, SIADH – syndrome of inadequate antidiuretic hormone secretion

treatment of patients with schizophrenia, affecting 15 to 72% of these patients (11).

There is, however, a hierarchy for risk of weight gain among antipsychotics, that has been confirmed in different studies and meta-analyses (11,23-33). Weight gain is greatest with the second-generation antipsychotics (SGAs) clozapine and olanzapine, while quetiapine, risperidone, paliperidone and iloperidone have an intermediate risk. Aripiprazole, amisulpride, ziprasidone, asenapine and lurasidone have less or little effect on body weight (11) (Table 2), although observed effects depend on the degree of prior treatment exposure (30). In children and adolescents (<18 years old), roughly the same hierarchy for risk of weight gain with these agents has been identified (23,34-36), yet at a higher level, likely due to less prior antipsychotic exposure (30). Among the first-generation antipsychotics (FGAs), the so-called low-potency agents, such as chlorpromazine and thioridazine, have higher weight gain potential than the high-potency drugs, such as haloperidol (11,30).

No antipsychotic, however, should be considered truly weight neutral, as the proportion of individuals experiencing significant weight gain is greater with any SGA than

with placebo (11,31). Antipsychotic-naïve or first-episode patients are more vulnerable to weight gain, as all antipsychotics have been found to cause significant weight gain in these patients (24). Moreover, antipsychotics have been found to produce more severe weight gain in these patients compared to those with chronic schizophrenia (37).

Generally, weight gain with antipsychotics is rapid during the first few weeks, slows gradually, and often reaches a plateau within one year (23). Results indicate that the first year of antipsychotic treatment is a critical period for weight gain and metabolic abnormalities (38), as initial rapid weight gain is a good indicator for long-term weight gain and obesity (23,39). According to a recent meta-analysis (24), almost all antipsychotics show a degree of weight gain after prolonged use, except for amisulpride, aripiprazole and ziprasidone. This meta-analysis also documented that switching subjects to metabolically more neutral compounds may not result in weight loss in all cases.

Antidepressants, such as amitriptyline and mirtazapine, and mood stabilizers, such as lithium and valproate, have also been associated with weight gain (23,40,41) (Table 2). However, weight gain is generally more modest or mild with antidepressants and mood stabilizers, and differences between antidepressants are modest (40).

Clinical and animal study data suggest that increasing appetite and food intake, as well as delayed satiety signaling, are key behavioral changes to antipsychotic-induced weight gain/obesity (24,39,42). Antagonism at 5-HT_{2C} and H₁ receptors seems involved in antipsychotic-induced weight gain. Among antipsychotics, clozapine and olanzapine, which have the highest weight gain/obesity risk, also have the highest affinities for 5-HT_{2C} and H₁ receptors (39).

There are marked individual variations in weight gain, irrespective of prescribed antipsychotic (39): some subjects lose weight, others maintain or gain weight with the same agent (24). Although (partial) non-adherence can be a confounder, this observation, together with the results from monozygotic twin and sibling studies, suggests that genetic factors play an important role in medication-induced weight gain (43-45), with estimates as high as 60-80% for antipsychotic-related weight gain (46).

Dyslipidemia

Antipsychotics have been associated with lipid abnormalities to relevant degrees (11,30) (Table 2). Adverse effects on triglycerides and cholesterol occur early and may even precede weight gain, pointing to weight-independent, molecular effects in addition to weight-related ones (30).

Compared to age- and sex-matched general population cohorts, metabolic syndrome criteria for elevated triglycerides (OR = 2.73, 95% CI: 1.95-3.83) and decreased high-density lipoprotein (HDL) cholesterol (OR = 2.35, 95% CI: 1.78-3.10) were more commonly met in patients with schizophrenia (17). Moreover, in chronic antipsychotic

Table 2 Adverse effects of antipsychotics, antidepressants and mood stabilizers on specific physical health outcomes

Physical disease/condition	Antipsychotics	Antidepressants	Mood stabilizers
Nutritional and metabolic diseases			
Obesity	0/+ (haloperidol, lurasidone, ziprasidone, aripiprazole) to +++ (clozapine, olanzapine, low potency FGAs)	– (bupropion) to + (mirtazapine, paroxetine, TCAs)	0 (lamotrigine) to ++ (valproate, lithium)
Dyslipidemia	+ to ++	0 to + (if weight gain)	– (valproate: cholesterol) to +
Endocrine system diseases			
Diabetes	0/+ (haloperidol, lurasidone, ziprasidone, aripiprazole) to +++ (clozapine and olanzapine > low and mid potency FGAs)	0 to +	0 to ++ (valproate)
Thyroid disorders	0	0	0 to ++ (lithium)
Hyponatremia/SIADH	+	+ to ++ (SSRIs)	0 to +
Cardiovascular diseases			
Hypertension	0 to ++	0 to + (venlafaxine)	0
Coronary heart disease and stroke	+ to ++	0 to +	0 to +
Myocarditis	0 to + (clozapine)	0	0
QTc prolongation/ sudden cardiac death	0 to + (thioridazine > sertindole > ziprasidone)	0 to + ?	0
Respiratory tract diseases			
Pneumonia	+ to ++ (clozapine)	0	– (lithium) to 0
Gastrointestinal diseases			
Constipation	0 to ++ (clozapine)	0 to + (TCAs)	0
Liver dysfunction	0 to ++ (often early and transient)	+	0 to ++ (valproate > carbamazepine)
Neoplasms			
Breast cancer	0 to + ?	0	0
Prolactinoma	0?	0	0
Musculoskeletal diseases			
Osteoporosis/fractures	0 to + (prolactin-raising antipsychotics)	+	– (lithium) to 0
Hematologic diseases			
Leucocytopenia/agranulocytosis	+ to +++ (clozapine)	0 to +	0 to ++ (carbamazepine)
Thrombocytopenia	0	0	0 to ++ (valproate)
Other physical diseases			
Kidney diseases	0	0	0 to ++ (lithium)
Movement disorders	+ to +++	0 to +	0 to +
Seizure disorders	+ to ++ (clozapine)	0 to + (TCAs > bupropion)	– to + (lithium toxicity)

– = reduction; 0 = likely/generally no effect; + = some effect; ++ = moderate effect; +++ = marked effect, ? = questionable

SIADH – syndrome of inadequate antidiuretic hormone secretion, FGAs – first-generation antipsychotics, SSRIs – selective serotonin reuptake inhibitors, TCAs – tricyclic antidepressants

treated patients, compared to first-episode or untreated patients with schizophrenia, metabolic syndrome criteria were more commonly met for elevated triglycerides (19.6%

and 16.9% vs. 41.1%) and low HDL cholesterol (21.9% and 20.4% vs. 44.7%) (17). An elevated risk for meeting the triglyceride and HDL cholesterol criteria for metabolic

syndrome was also found in patients with depression (22) and bipolar disorder (47), with higher metabolic syndrome risk in populations receiving antipsychotics.

Although some antidepressants have been associated with weight gain (23,41), which is a risk factor for lipid abnormalities, data on adverse lipid effects of these medications remain scarce, and most antidepressants have not been associated with dyslipidemia (48) (Table 2).

Among mood stabilizers, lithium has not been associated with relevant lipid abnormalities (49), although lithium-induced hypothyroidism can lead to weight gain and changes in lipid profile (50). Valproate has been associated with reductions in total and low-density lipoprotein (LDL) cholesterol in patients with schizophrenia (51) and bipolar disorder (52), despite its association with weight gain, increased triglycerides and glucose, and insulin abnormalities (53) (Table 2).

ENDOCRINE SYSTEM DISEASES

Diabetes mellitus

Evidence suggests that the prevalence of type 2 diabetes mellitus (DM) in people with schizophrenia, bipolar disorder and schizoaffective disorder is 2-3 fold higher than in the general population (9,16,25,39,54,55). Two meta-analyses found overall prevalences of DM in people with multi-episode psychosis to be 9.5% (N = 116,751) (16) and 12.8% (N = 2,098) (56), respectively, nearly twice as high as in the general population (9). The risk of type 2 DM in people with (major) depression or depressive symptoms is 1.2-2.6 times higher than in those without depression (11,57). The age of onset of DM in individuals with a SMI seems to be about 10-20 years earlier than in the general population (58,59).

An association, albeit of uncertain magnitude, seems to exist between antipsychotics and DM, affecting about 12% of people receiving these medications (9). Recently, meta-analyses (16,56) showed that the prevalence of DM is not appreciably increased in drug-naïve patients during the first episode of psychosis once control groups are age-matched. The majority of studies suggest that metabolic abnormalities accumulate rapidly after the initiation of treatment (9,30).

Although a former meta-analysis showed that SGAs seem to have a stronger diabetogenic risk than FGAs, the risk being 1.3 fold higher in people with schizophrenia taking the former compared with those receiving the latter medications (60), a more recent meta-analysis indicated that, at the moment, evidence is still insufficient to draw firm conclusions about the relative risk of SGAs and FGAs (61). However, this uncertainty may well be due to the fact that neither of the two classes is homogeneous regarding cardiometabolic risk. Several studies suggest that the differing weight gain liability of SGAs contribute to the differing relative risks (RRs) of DM with these agents: specifically,

olanzapine and clozapine, and to a lesser extent quetiapine and risperidone, were shown to be associated with an increased risk of glucose dysregulation or DM in people who have schizophrenia or bipolar disorder (28,62) (Table 2).

Nielsen et al (63) showed DM development in first-episode schizophrenia patients initially treated with olanzapine (hazard ratio, HR = 1.41) and mid-potency FGAs (HR = 1.60). During longer-term treatment and adjusting for follow-up duration, DM was associated with low-potency FGAs (OR = 1.45), olanzapine (OR = 1.57) and clozapine (OR = 2.31). Fleischhacker et al (64) found, in first-episode schizophrenia patients, newly diagnosed cases of DM with olanzapine and amisulpride during a 52-week treatment period.

Antipsychotics should be used with caution in children and youth (65). A recent study (66) found a 3-fold increased risk of DM in children and youth (the most frequently recorded psychiatric diagnoses were mood disorders, attention-deficit/hyperactivity disorder and conduct disorder) who had recently initiated antipsychotic treatment (HR = 3.03, 95% CI: 1.73-5.32), compared to those receiving other psychotropic medications. The risk was already increased within the first treatment year (HR = 2.49, 95% CI: 1.27-4.88), increased further with cumulative dose, and remained elevated one year after antipsychotic discontinuation (HR = 2.57; 95% CI: 1.34-4.91) (67).

Antipsychotics may induce DM independent of weight gain and adiposity (39,42). Thus, a model in which antipsychotic-induced DM is solely due to obesogenic effects is an oversimplification (42). These medications appear to contribute to DM both indirectly, by inducing weight gain, and directly, by promoting insulin resistance. M3 receptors play a crucial role in the regulation of insulin secretion through both peripheral and central cholinergic pathways (39). Therefore, DM induced by SGAs may be partly due to the blockade of central and peripheral M3 receptors. Olanzapine and clozapine, the SGAs with the highest risk to induce DM, also possess the highest M3 receptor-binding affinity (40). M3 blockade may lead to an initial disruption of insulin secretion and glucose homeostasis that can progressively lead to insulin resistance and DM during chronic treatment (67).

The literature is still inconclusive on a possible association between antidepressants and DM (23,68-71). Several reports (68,72-75) suggest that the (concurrent) use of (certain) antidepressants is associated with an increased risk of glucose dysregulation or DM; others do not (76,77) (Table 2).

A recent meta-analysis (78) found that antidepressants increased the likelihood of new-onset DM (OR = 1.50, 95% CI: 1.08-2.10; HR = 1.19, 95% CI: 1.08-1.32). However, because only observational studies were included in this analysis, a causal relationship could not be established (71,78). Long-term randomized controlled and prospective studies are needed to confirm a possible cause-effect relationship. Another problem is that (major) depression may

act as a confounding variable in the relationship between antidepressants and DM risk: antidepressants may have an impact on mental illness-related factors relevant to the risk for DM, such as physical activity and diet (71,79).

Nevertheless, there are indications that an increased risk of DM is associated with the concurrent use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) (OR = 1.89) (80), the long-term use of either tricyclic antidepressants (incidence rate ratio, IRR = 1.77) or SSRIs (IRR = 2.06) in at least moderate daily doses (81), and the use of antidepressants in high-risk patients (82).

Some reports (57) also indicated that the use of mood stabilizers is associated with DM (OR = 1.64) in patients with major depression. Indeed, certain mood stabilizers, especially valproate, have been associated with an elevated risk for the development of insulin resistance (83) (Table 2).

Diabetic ketoacidosis

Although diabetic ketoacidosis (DKA), a potentially fatal condition (84), occurs most often in patients with type 1 DM (85), it may be the first obvious manifestation of type 2 DM. Physical symptoms include: increased thirst (polydipsia) and urination (polyuria), excessive appetite (polyphagia), nausea, abdominal pain and vomiting, dehydration, Kussmaul breathing, acetone (“fruity apple-like”) breath, weakness or lethargy, confusion and altered consciousness (85).

The incidence of DM presenting as DKA is, compared to the general population, nearly 10-fold higher in patients with schizophrenia (86). Cases of DKA in patients not previously known to be diabetic, including several fatalities, have been associated with SGA treatment initiation (54,86). While the underlying mechanisms are not well understood, antipsychotic-related DKA can occur soon after treatment onset and in the absence of weight gain (over one third of cases presented with either no weight gain or even weight loss) (85).

DKA can occur with almost all SGAs. However, at least half of the reports involve individuals on polypharmacy, complicating the risk attribution to a specific antipsychotic (85). The greatest number of DKA cases has been observed with clozapine and olanzapine. However, cases have also been reported with quetiapine, risperidone, and even with aripiprazole and ziprasidone (85,87), although order or channelling effects (i.e., shifting high-risk patients to lower risk agents) cannot be excluded.

Although DKA remains a rare adverse effect of SGAs, clinicians must remain vigilant, given its acute onset and potential lethality (85).

Hypothyroidism and hyperparathyroidism

Hypothyroidism is a common adverse effect of lithium, warranting continued monitoring (Table 2). A recent sys-

tematic review (40) concluded that, compared to placebo, lithium is associated with increased thyroid stimulating hormone (TSH) levels (+4.00 iU/mL, 95% CI: 3.9-4.1) and clinical hypothyroidism (OR = 5.78, 95% CI: 2.00-16.67).

In addition, lithium can produce adverse effects on the parathyroid gland. Compared with placebo, lithium was associated with increased parathyroid hormone (+7.32 pg/mL, 95% CI: 3.42-11.23) and blood calcium (+0.09 mmol/L, 95% CI: 0.02-0.17), but effects are generally mild (40).

Although quetiapine has been associated with mild T4 elevations, TSH levels were within normal limits and patients remained euthyroid (88).

Other antipsychotics, antidepressants, valproate and carbamazepine do not seem to affect thyroid or parathyroid functioning (Table 2).

Syndrome of inappropriate antidiuretic hormone secretion and hyponatremia

Antipsychotics appear to be associated with an increased prevalence of hyponatremia (89,90), which is often associated with polydipsia (Table 2).

Antidepressants, especially SSRIs, have been associated with the syndrome of inappropriate antidiuretic hormone secretion and with hyponatremia (91) (Table 2). In a recent systematic review (92), that was limited by variations in study designs, populations, and utilized thresholds, the incidence of hyponatremia diverged between 0.06% and 40% for SSRIs and between 0.08% and 70% for venlafaxine. Incidences for mirtazapine and tricyclic antidepressants were lower, and ORs for SSRIs (1.5-21.6) were consistently higher than for tricyclic antidepressants (1.1-4.9), but much less evidence was available for non-SSRI antidepressants. Identified patient risk factors included older age (OR = 6.3) and concomitant use of (thiazide) diuretics (OR = 11.2-13.5) (92). Carbamazepine and valproate have been associated with hyponatremia in case reports.

Based on the above, electrolytes should be checked in patients on antipsychotics, antidepressants and/or mood stabilizers with otherwise unexplained physical or mental state deterioration (Table 2).

CARDIOVASCULAR DISEASES

Hypertension

Although antipsychotics increase body weight and are associated with obesity, their effect on blood pressure is less pronounced than expected. This has likely to do with their alpha-1 blocking effects (93), which can lower blood pressure. Nevertheless, hypertension criteria for metabolic syndrome are more commonly met in patients with schizophrenia than in the general population (OR = 1.36, 95% CI: 1.21-1.53) (16), as well as in chronic patients with schizo-

phrenia receiving antipsychotics (39.7%) than in first-episode (30.4%) or untreated patients (24.3%) (56). Elevated risk for meeting the hypertension criterion for metabolic syndrome was also found in patients with depression (22) and bipolar disorder (47), with higher metabolic syndrome risk in populations receiving antipsychotics (Table 2).

Among antidepressants, venlafaxine is the one most frequently associated with increase in blood pressure (94), while mirtazapine has been found to be associated with hypertension less than tricyclic antidepressants (95) (Table 2). Generally, mood stabilizers do not affect blood pressure, unless chronic renal failure induced by lithium affects volume distribution (Table 2).

Coronary heart disease and stroke

The preponderance of evidence suggests that patients with schizophrenia, bipolar disorder and major depression are at significantly higher risk for cardiovascular morbidity and mortality than their counterparts in the general population (1,5,6,11,96-99). The risk is approximately 1.5 to 3-fold increased in patients with schizophrenia and bipolar disorder, and on average 1.5-fold increased in those with major depression. Moreover, cardiovascular diseases are the commonest cause of death in patients with SMI (100,101), with risks 10-fold higher than suicide (102). The literature on antipsychotic-related cardiovascular outcomes in patients with a SMI is sparse. Moreover, data are conflicting.

Although some studies (103,104) reported a higher risk of cerebrovascular diseases in patients using antipsychotics, others (105) did not (Table 2). In case-control studies with elderly patients, the probability of cerebrovascular accidents in antipsychotic users, compared with non-users, was approximately 1.3- to 2-fold greater (106). The risk of stroke is highest during the first weeks of treatment (104,106). A recent meta-analysis of 20 observational cohort studies found that older adults (≥ 65 years) using FGAs were not at a statistically significantly increased higher risk (RR = 1.4; 95% CI: 0.81-1.91) for stroke, as compared to SGA users (107).

Few studies have looked at the association between antipsychotics and myocardial infarction, which remains controversial because of heterogeneous clinical settings and methodological approaches (108,109). Some found an increased risk of myocardial infarction in older patients (≥ 66 years) with or without dementia (110,111) or patients with SMI (109,112) using antipsychotics compared to control subjects (RR = 1.15-6.2) (110,111). In the study by Lin et al (109), carried out in a large sample of patients with schizophrenia, mood disorders or dementia, the adjusted OR of acute myocardial infarction risk was 2.52 (95% CI: 2.37-2.68) for any antipsychotic, 2.32 (95% CI: 2.17-2.47) for FGAs, and 2.74 (95% CI: 2.49-3.02) for SGAs. A recent meta-analysis found that older adults (≥ 65 years) using FGAs were at higher risk for myocardial infarction (RR =

1.2; 95% CI: 1.16-1.23) compared to SGA users (107). However, several other studies (e.g., 112) found no significant association between the risk of myocardial infarction and antipsychotic exposure.

The risk for cardiovascular events varies with the individual SGAs. This risk seems to be lowest with aripiprazole and ziprasidone (113-115). Considering FGAs, a nationwide, register-based, five-year follow-up study of all patients presenting with first onset of schizophrenia found an increased likelihood for cardiovascular deaths among users of levomepromazine (OR = 2.68; 95% CI: 1.37-5.25, $p = 0.004$) (116).

Data on the comparative acute cardiovascular safety of SGAs in younger adults are limited. In a recent large nationwide register-based cohort study (N = 48,625) (117), the risk of major cardiovascular events (cardiovascular mortality, acute coronary syndrome or ischemic stroke) in non-elderly (18-64 years) psychiatric outpatients was similar with risperidone, olanzapine and quetiapine within one year of treatment initiation. In another recent commercial U.S. claims database inception cohort study of 284,234 non-elderly adults aged 18-65 years (118), individuals within one year of exposure to SGAs showed a higher risk of essential hypertension (adjusted HR, AHR = 1.16, 95% CI: 1.12-1.21), DM (AHR = 1.43, CI: 1.33-1.53), hypertensive heart disease (AHR = 1.34, CI: 1.10-1.63), stroke (AHR = 1.46, CI: 1.22-1.75), coronary artery disease (AHR = 1.17, CI: 1.05-1.30), and hyperlipidemia (AHR = 1.12, CI: 1.07-1.17) than those exposed to antidepressants.

Compared to obese individuals without a SMI, obese patients with SMI have a significantly higher cardiovascular risk (119). This raises the possibility that, in addition to weight gain and obesity-related mechanisms, a direct effect of antipsychotics on cardiovascular risk may exist. For example, autonomic nervous system dysfunction triggered by schizophrenia may be exacerbated by antipsychotic treatment through blockade of peripheral dopamine receptors, increasing sympathetic activity (120). A direct effect of antipsychotics on insulin resistance, causing glucose intolerance, is another possible mechanism contributing to the increased risk of cardiovascular diseases (121).

The potential cardiovascular effects of tricyclic antidepressants are well known. They can cause orthostatic hypotension, slowed cardiac conduction, and increased heart rate, and are therefore best avoided in patients with pre-existing cardiovascular disease (122). SSRIs appear to have a better cardiovascular safety (123,124) (Table 2). Nevertheless, in patients with high risk factors, SSRIs (i.e., citalopram) (125,126) may be associated with (modest) QTc prolongation. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with a small, but increased incidence of cardiovascular adverse events (hypertension, tachycardia and orthostatic hypotension), while at therapeutic doses they do not seem to cause QTc prolongation (122). Although lithium can have some cardiac conduction effects, in general, it can be used safely in patients with cardiac disease (123) (Table 2).

Myocarditis

Myocarditis is a potential risk of clozapine treatment, occurring often early in treatment and in young male patients (127). Therefore, routine electrocardiographic monitoring for the first four weeks, and discontinuation of clozapine in the presence of myocarditis, may assist to prevent fatalities (128). However, case reports suggest that rechallenge with clozapine using slow titration may be successful in the majority of reported cases (129).

Sudden cardiac death

Patients with schizophrenia have been reported to be 2-4 times more likely to experience sudden cardiac death (SCD) than the general population (130,131). Although reasons for this increased risk remain unclear, individual susceptibility (e.g., underlying coronary artery disease (101) and higher prevalence of Brugada electrocardiographic abnormalities (131)) seems to be a relevant factor. Additional important risk factors include unhealthy lifestyle factors and psychotropic medications.

The association between SCD and specific psychotropic drugs has been explained by a lengthening of ventricular repolarization (QTc prolongation), predisposing the patient to life-threatening ventricular tachyarrhythmias (i.e., torsades de pointes, TdPs) (132). There is a consensus that QTc values >500 msec, or an absolute increase of ≥ 60 msec compared with drug-free baseline, puts patients at significant risk of TdPs and SCD (126,133). However, although a link exists between QTc and TdPs, this is neither linear, nor straightforward (126). Indeed, TdPs can occur at therapeutic doses of antipsychotics or antidepressants with a QTc interval <500 ms (134).

Patients using FGAs or SGAs have an increased risk of SCD compared to non-users with or without a psychiatric illness, with ratios ranging from 1.5 to 5.8, depending on the type of antipsychotic and restrictiveness of the SCD definition (11,131,135,136). The largest study to date (459,614 incident antipsychotic users) reported a SCD incidence of 3.4 per 1,000 person-years (137). Antipsychotics with a greater risk of QTc prolongation include thioridazine (greatest risk), pimozide, droperidol, mesoridazine, and i.v. haloperidol (total cumulative dose >2 mg) among FGAs (126,133), and sertindole, amisulpride and ziprasidone among SGAs (32,133). QTc prolongation with lurasidone and aripiprazole is judged to be clinically insignificant (32,133). QTc prolongation associated with asenapine and iloperidone is comparable to that associated with risperidone, olanzapine and quetiapine (32,133) (Table 2).

According to a recent meta-analysis, SSRIs are, compared to placebo, associated with a statistically significant (but clinically insignificant for most patients) dose-dependent increase in the QTc interval (+6.10 milliseconds; 95% CI: 3.47-8.73, $p < 0.001$) (125). The highest effect seems to

be associated with citalopram (138). Tricyclic antidepressants prolong the QTc interval to a greater extent than SSRIs by a factor of more than 2 (125).

Studies linking antipsychotics and antidepressants with an increased SCD risk suggest a dose-dependent relationship (135,139).

Cases of TdPs have been reported with antipsychotics, tricyclic antidepressants and SSRIs. Using the FDA Adverse Event Reporting System (FAERS) data, the Arrhythmogenic Potential of Drugs (ARITMO) project (140,141) classified, next to ziprasidone, five other SGAs (amisulpride, clozapine, olanzapine, quetiapine and risperidone) as having a very strong torsadogenic signal. However, these antipsychotics (with the exception of amisulpride and possibly quetiapine) have, in general, been associated with a QTc prolongation potential of questionable clinical concern (133). SSRI-associated TdP is a very rare event: only very few cases have been reported (142). However, adding SSRIs to SGAs may, although also very rarely, contribute to TdPs (143). There are no reported cases of lithium-induced TdPs (139).

Notably, coronary heart disease underlies the majority of SCD (144). A recent recommendation concludes that it is not mandatory to perform electrocardiogram monitoring as a prerequisite to initiating antipsychotic treatment in the absence of cardiac risk factors, unless the prescribed antipsychotic has been established to have an increased risk of TdP and SCD (133) (Table 2).

RESPIRATORY TRACT DISEASES

Pneumonia

One century ago, respiratory diseases, such as pneumonia and tuberculosis, accounted for the majority of deaths amongst people with SMI who lived in institutions (145). Today, they are still more prevalent in these individuals compared to the general population, and among the most common causes of death (146-149).

Not only having a SMI, but also the use of psychotropics is a risk factor for respiratory tract diseases. A dose-dependent increased risk for pneumonia is associated with current use of SGAs in patients with schizophrenia (adjusted RR, ARR = 1.69, 95% CI: 1.43-2.01 vs. non-users) (150,151) and bipolar disorder (ARR = 2.07, 95% CI: 1.58-2.71 vs. non-users) (152). Similarly, the current use of SGAs and FGAs in elderly patients without a SMI seems to be associated with a dose-dependent increase in the risk for pneumonia (153-157).

In patients with schizophrenia, particularly the current use of clozapine is associated with an elevated and dose-dependent risk of pneumonia (ARR = 3.18, 95% CI: 2.62-3.86, $p < 0.001$), while this risk is moderate for olanzapine, quetiapine and risperidone (ARR between 1.32 and 1.83, $p < 0.001$), compared to patients not currently using anti-

psychotics (150) (Table 2). In patients with bipolar disorder, the current use of clozapine (ARR = 2.59, $p < 0.01$), as well as the current use of olanzapine and haloperidol, were associated with dose-dependent risk ratios for pneumonia greater than 2.50. Furthermore, pneumonia had a longer duration in these patients during the period of exposure to each of these drugs (151).

With antidepressants, no increased risk of pneumonia has been found in most studies (e.g., 158) (Table 2).

There seems to be no significant association between mood stabilizers and pneumonia, and lithium even has a dose-dependent protective effect (152) (Table 2). However, the combination of mood stabilizers and SGAs or FGAs was associated with an increased risk. Among drug combinations, olanzapine plus carbamazepine had the highest risk (ARR = 11.88, $p < 0.01$), followed by clozapine plus valproic acid (RR = 4.80, $p < 0.001$) (152).

Although the possible mechanisms of drug-induced pneumonia remain speculative (153), H1 antagonism by clozapine and olanzapine, inducing sedation, and M1 antagonism, inducing dryness of the mouth, esophageal dilatation and hypomotility, may be involved, as well as the additive sedating effect by carbamazepine or valproic acid (152).

GASTROINTESTINAL DISEASES

Liver diseases

Liver function test abnormalities in patients receiving antipsychotics are common, but often mild and transient. According to a systematic review (159), the median percentage of patients with any abnormal liver function test on any antipsychotic was 32% (range: 5-78%). However, the median percentage of patients with clinically significant elevations (i.e., > 3-fold above the upper limit of normal for alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase or > 2-fold the upper limit of normal for alkaline phosphatase) was 4% (range: 0-15%) (Table 2). Abnormalities were generally asymptomatic, arose within 6 weeks of starting an antipsychotic, and did not worsen or resolved with continued treatment. The most commonly abnormal liver function test involved transaminases, and there was no clear difference between FGAs and SGAs.

Rarely, antipsychotics have been associated with severe or fatal hepatic injury. The FGA chlorpromazine has been most widely implicated with severe cholestatic hepatic injury. There are three main mechanisms by which antipsychotics can be associated with liver injury: by impairing bile secretion, leading to cholestasis; by exerting a direct toxic effect on hepatocytes; and by affecting the liver indirectly via obesity leading to non-alcoholic fatty liver disease (159).

Between 0.5 and 3% of patients receiving antidepressants may develop asymptomatic mild elevation of serum aminotransferase levels. However, all antidepressants can induce hepatotoxicity, especially in elderly patients and those on

polypharmacy (Table 2). The antidepressants with the highest risk of hepatotoxicity include iproniazid, nefazodone, phenelzine, venlafaxine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine and agomelatine (160-162). Those with the least potential include citalopram, escitalopram, paroxetine and fluvoxamine (162). Monitoring of liver function tests and immediate discontinuation upon emergence of abnormal laboratory findings or signs/symptoms of liver dysfunction are crucial, since most cases of hepatic damage are reversible when detected early (162).

Among mood stabilizers, carbamazepine and valproate have been associated with liver dysfunction and should be avoided in patients with pre-existing liver disease (163) (Table 2).

Constipation

Severe constipation leading to serious consequences and even death can occur with certain antipsychotics. The most reported complications are paralytic ileus, faecal impaction, bowel obstruction and intestine/bowel perforations (164).

Constipation has been most widely reported with clozapine (123,164), although it can be associated with other antipsychotics as well (165) (Table 2). The prevalence of constipation in randomized controlled trials is 39.6% with zotepine, 21.3% with clozapine, 14.6% with haloperidol and 12% with risperidone (166).

Constipation is a common side effect of tricyclic antidepressants, while it is not particularly associated with exposure to mood stabilizers (Table 2).

HAEMATOLOGIC DISEASES

Leucocytopenia and agranulocytosis

Antipsychotics (especially but not only clozapine), antidepressants (e.g., clomipramine and imipramine) and mood stabilizers (especially carbamazepine) have been associated with leucocytopenia and agranulocytosis (167-170) (Table 2).

Clozapine (particularly in the first three months of treatment) and phenothiazines are the most common causes of drug-related neutropenia/agranulocytosis (169). The risk for neutropenia and agranulocytosis with clozapine is approximately 3% and 1%, respectively, with older patients being at higher risk (167,168). Carbamazepine should not be used in combination with clozapine, due to its potentiation of neutropenia and agranulocytosis (169,170). Anti-infective agents, proton pump inhibitors and other gastrointestinal agents have also been associated with haematological adverse effects when co-prescribed with clozapine (171). Non-tricyclic antidepressants are rarely associated with agranulocytosis.

With appropriate management, the mortality from drug-induced agranulocytosis in Western countries is currently approximately 5% (decreasing from 10-16% over the past two decades) (167).

Thrombocytopenia

Among the reviewed psychotropic drug classes, only valproate has been associated with thrombocytopenia to a relevant degree (Table 2). The incidence may be around 5%, and more likely at valproate serum levels above 80 mcg/ml, especially in females and older people (172).

NEOPLASMS

Breast cancer

Generally, patients with SMI, especially schizophrenia, have lower cancer rates than the general population (173), despite unhealthy lifestyle and a higher likelihood of obesity. However, this comparison is complicated by the fact that most cancers accumulate with age and that people with SMI die on average 15-25 years earlier than the general population (11).

Breast cancer is one of the most commonly diagnosed cancers worldwide (one in eight women will be diagnosed with this cancer during their lifetime), is the leading cause of cancer death among females, and starts occurring in early adulthood (174-176). Given that women with schizophrenia have lower parity (177,178) and higher frequencies of other known breast cancer risk factors (obesity, DM, unhealthy lifestyle behaviors, including alcohol dependence and smoking), one would anticipate higher breast cancer rates in this population. However, data are conflicting. Although several studies have shown an increased breast cancer risk and mortality rate among women with schizophrenia (e.g., 173,179-182), other studies have found a decreased or a statistically non-significantly increased risk (e.g., 183,184) (Table 2). A recent meta-analysis of observational studies in people with central nervous system disorders found that patients with schizophrenia showed a higher co-occurrence of breast cancer (effect size = 1.25; 95% CI: 1.10-1.42) (185).

Increasing experimental and epidemiological data point to the influence of prolactin in mammary carcinogenesis (186), raising questions about the possible relationship between prolactin-raising antipsychotics and breast cancer risk. The current evidence base, however, is very limited. The majority of studies focused on patients treated with FGAs (186), not finding an increased breast cancer risk. An exception is the cohort study by Wang et al (187), in which 52,819 women on antipsychotic dopamine antagonists were compared with 55,289 women who were not on antipsychotics. The authors found that, compared with

non-users, women who used antipsychotic dopamine antagonists had a 16% greater risk (AHR = 1.16, 95% CI: 1.07-1.26) of developing breast cancer, with a direct dose-response relationship. As stated by the authors, the magnitude of the observed risk, although statistically significant, was small in absolute terms (1,239 cases of breast cancer in the user group versus 1,228 cases in the non-user group). Furthermore, it was estimated that there is less than a 14% chance that a dopamine antagonist user who develops breast cancer does so on the basis of her antipsychotic use. The authors therefore concluded that their findings “do not warrant changes in patients’ antipsychotic medication regimens” (187, p. 1153).

Among SGAs, there has been concern that risperidone, amisulpride and paliperidone, which have been associated with hyperprolactinemia (188), may increase the risk of breast cancer. However, so far, results indicate that these compounds do not seem to increase this risk (189).

A systematic review (190), including 93 studies (*in vitro*, animal and human studies) considering the effects of antipsychotics (FGAs + SGAs) on cancer development, found that these medications as a class cannot be considered as a risk factor for breast cancer in humans. Moreover, some reports describe mechanisms of cancer protection with antipsychotics (or antidepressants) (186,191,192). For example, it has been shown *in vitro* that (prolactin-elevating) phenothiazines may enhance the effect of tamoxifen, a first-line adjuvant treatment for breast cancer patients, in human breast cancer cells (193,194). Thus, to date, no robust evidence exists for an increased risk of breast cancer due to antipsychotic-induced hyperprolactinemia (186,195).

As evidence suggest that SSRIs can increase circulating prolactin above the accepted normal range (20 ng/ml in men and 25 ng/ml in women) (196-198) via prolactin releasing factors, such as vasoactive intestinal peptide and oxytocin (188), antidepressant-related breast cancer risk has been questioned. Overall, however, results do not support the serotonin-mediated pathway for the prolactin-breast cancer hypothesis, irrespective of the type of antidepressant (198-200) (Table 2).

Prolactinoma

Although a pharmacovigilance study raised concern about a possible association between prolactin-raising antipsychotics and prolactinomas (201), evidence for a causal relationship is missing (Table 2). Potential reasons for the observational association include a background rate of 5-10% of silent prolactinomas that are more likely detected when elevated prolactin levels prompt brain imaging studies, and the potential misclassification of pituitary hypertrophy related to prolactin elevation due to antipsychotics as prolactinoma (188). In patients with secreting prolactinomas and psychosis, the partial D2 agonist aripiprazole may be particularly useful (202).

MUSCULOSKELETAL DISEASES

Osteoporosis

Schizophrenia and bipolar disorder are associated with lower bone mineral density (BMD) and higher prevalence of osteoporosis compared to the general population (203-206). The etiology of BMD loss in these patients is complicated (204,207). Risk factors related to patients' lifestyle (e.g., smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, polydipsia) (203), as well as use of antipsychotics (207,208), are likely to be involved. Several reviews and meta-analyses (209-213) have reported that (major) depression is also associated with low BMD and increased fracture risk.

Although raised prolactin levels induced by antipsychotics have been associated with an increased risk of osteoporosis (214) (Table 2), clinical data implicating antipsychotic-induced hyperprolactinemia as a possible major risk factor for bone loss remain limited and contradictory (203,204). One review (203) showed that 60% of the studies examining the relationship between antipsychotic-induced hyperprolactinemia and BMD loss found some effects of hyperprolactinemia. However, samples and effects were small, and only few studies were prospective. The increased risk for bone loss induced by hyperprolactinemia is believed to be mediated by hypogonadism (215), leading to abnormally low sex hormone levels, although some evidence suggests direct effects of prolactin on human osteoblasts (216).

Most studies and reviews (157,203,217-223) found significant increases in the risk of fractures (ORs between 1.2 and 2.6) associated with antipsychotics. Compared with SGAs, a higher fracture risk was found for FGAs in some studies (158,220,224), possibly due to extrapyramidal symptoms causing gait disturbances and impairing mobility and balance, which are risk factors for falls (and, thus, fractures) in older adults (107). However, other studies (105,219,225) found no differences between FGAs and SGAs. Moreover, it is also unclear whether individual SGAs differ in the risk of falls/fractures (105,218,226).

Longitudinal, cross-sectional and prospective cohort studies, as well as meta-analyses, suggest that antidepressants, particularly SSRIs, at therapeutic doses are associated with decreased BMD and increased fracture risk, especially in older adults (218,220-222,227-249) (Table 2). Reduced BMD has also been found in young adults and children prescribed SSRIs (250,251). For SSRIs and tricyclic antidepressants, a growing excess risk of fractures has been reported with increasing dose (227,233,235), although this effect does not appear to be homogeneous across the whole class of drugs (227). The increase in risk is highest during the early stages of treatment, with a dramatic increase after initiation, reaching a peak within one month for tricyclics and eight months for SSRIs (228), decreasing towards baseline following discontinuation (227,228).

The most recent meta-analysis (237), which pooled results from 13 qualifying cohort and case-control studies, found that SSRIs were associated with a significantly increased risk of fractures (RR = 1.72, 95% CI: 1.51-1.95, $p < 0.001$). This increased risk was also observed in studies that adjusted for depression (RR = 1.74, 95% CI: 1.28-2.36, $p < 0.001$) and for BMD (RR = 1.70, 95% CI: 1.28-2.25, $p < 0.001$). Treatment with SSRIs seems also to be associated with an increased failure of bone implants, which suggests the need for careful surgical treatment planning in SSRI users (252). The effect of SSRIs on bone formation and resorption appears to be governed by the activation of a number of 5-HT receptors on osteoblasts and osteoclasts via endocrine, autocrine/paracrine and neuronal pathways (241,253,254).

Lithium is possibly associated with a reduced fracture risk (255,256) (Table 2). Long-term treatment with valproate combined with low-dose SGAs may adversely affect BMD in premenopausal women with bipolar disorder (257). Finally, concomitant use of an opioid with one or several antipsychotics may also increase fracture risk in elderly patients (258,259).

OTHER PHYSICAL DISEASES

Kidney diseases

Nephrotoxicity is a well-known side effect of lithium (260) (Table 2). Acute renal failure has been described in lithium intoxication (261), but the greatest concern is the possible progression to end-stage renal disease during long-term use (262).

However, conflicting evidence concerning lithium's effect on renal function exists. A systematic review (263), investigating the effects of lithium on renal function in older adults, and the largest and most recent meta-analysis to date (40), screening nearly 6,000 publications on various aspects of potential lithium toxicity in patients with depression or bipolar disorder, both concluded that there is little evidence for a clinically significant reduction in renal function in most patients, and that the risk of end-stage renal failure is low. These results are consistent with a former meta-analysis (264). Nevertheless, end-stage renal failure only starts appearing in some patients after continuous treatment for more than 15-20 years, whereas meta-analyses include numerous patients treated for shorter periods (265). Moreover, several studies (266,267) on prolonged lithium treatment have suggested that the risk of renal end-stage failure might not be that low.

According to the International Group for the Study of Lithium-Treated Patients, approximately 25% of patients on medium-term lithium therapy (<15 years), as well as most patients on long-term lithium treatment (>15 years), develop some form of chronic lithium nephropathy (268). However, this condition manifests primarily as impaired urinary concentration with or without polyuria, which generally has

little clinical relevance. In contrast, patients with severe polyuria are at increased risk for lithium intoxication due to fluctuations in sodium levels. Effects of lithium intoxication range from minor tubular changes to acute tubular necrosis, which generally is reversible upon removal of excess amounts of lithium. Recurrent lithium intoxication, however, is thought to promote progressive lithium nephropathy (269). Thus, regular lithium level monitoring may protect against acute and chronic renal failure, and should be mandatory in long-term lithium-treated patients (269).

Movement disorders

In susceptible patients, chronic treatment with antipsychotics can lead to movement disorders, including tardive dyskinesia, tardive dystonia and tardive akathisia (270) (Table 2). Although SGAs seem to have a 5- to 6-fold reduced risk for tardive dyskinesia compared to FGAs (271,272), the risk is not zero. Moreover, older people (273) and those with extrapyramidal symptoms or anticholinergic use (271) are at elevated risk for tardive dyskinesia.

Antidepressants, lithium and valproate are generally not associated with tardive dyskinesia (Table 2). Nevertheless, tremor and myoclonus, which can occur with lithium and valproate, respectively, can be mistaken for tardive dyskinesia. Moreover, movement disorders can also occur endogenously in patients with schizophrenia (274), and other medications, such as metoclopramide (275), also carry a risk for tardive dyskinesia.

Seizure disorders

All antipsychotics, especially clozapine, have the potential to reduce the seizure threshold (276,277). This effect is generally not clinically relevant, but is dose-dependent and rises sharply at clozapine doses of 500-600 mg/day, while relationships with clozapine blood levels are less clear (278). When seizures occur, this is not a reason to discontinue clozapine; rather, valproate should be added for seizure prophylaxis (adjusting the clozapine dose as needed) (127).

Antidepressants can also lower the seizure risk threshold (91,276), with intermediate epileptogenic potential for tricyclic antidepressants and lower epileptogenic potential for bupropion (277), which is still contraindicated in people with seizure disorders (Table 2). Being antiepileptic medications, valproate and carbamazepine reduce seizure risk, while lithium, which at lower doses may even be protective (279), can lead to seizures when reaching toxic levels.

CONCLUSIONS

Patients with SMI are at increased risk for physical diseases and related earlier mortality (11,280). Besides mental

illness-related factors, disparities in health care access and utilization, and unhealthy lifestyle, psychotropic medications can contribute to the emergence or aggravation of physical diseases. This review summarized recent evidence for the effect of antipsychotics, antidepressants and mood stabilizers on physical health/illness in patients with schizophrenia, major depression and bipolar disorder.

In general, adverse effects on physical health are greatest with antipsychotics, followed by mood stabilizers, tricyclic antidepressants and newer antidepressants. However, effects vary greatly among individual agents, and interactions with underlying host factors are relevant. Higher dosages, polypharmacy, and the treatment of vulnerable (e.g., old or young) people seems to be associated with a greater effect on most physical diseases.

Although antipsychotics have the greatest potential to adversely affect physical health, it is important to note that several large, nationwide studies providing generalizable data have suggested that all-cause mortality is higher in patients with schizophrenia not receiving antipsychotics (4,281). Furthermore, clozapine (4), antidepressants (282), and lithium (283), as well as antiepileptics (284), are associated with reduced mortality from suicide. Thus, the potential risks of antipsychotics, antidepressants and mood stabilizers need to be weighed against the risk of the psychiatric disorders for which they are used and the lasting potential benefits that these medications can produce.

Nevertheless, greater attention to the possible impact of psychotropic medications on the physical health of people with SMI can aid clinicians in selecting appropriate treatments for individual patients whose medication-independent risk factors for specific disorders require special consideration. Moreover, knowledge about specific medication effects can help implementing appropriate monitoring and management strategies aimed at improving physical and well as mental health outcomes of these generally disadvantaged populations.

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