Clinical and Practical **Psychopharmacology**

Use of Metformin for Cardiometabolic Risks in Psychiatric Practice: Need-to-Know Safety Issues

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Metformin, a biguanide drug, is emerging as an important treatment option for the prevention or treatment of weight gain, type 2 diabetes mellitus, and the metabolic syndrome in psychiatric patients, especially those who require or receive antipsychotic drugs. Metformin treatment is commonly associated with gastrointestinal adverse effects; the risk of these is reduced by gradual dose uptitration, administration of the drug with meals, and use of a time-release formulation. Lactic acidosis, a potentially fatal complication of biguanide therapy, is very rare with metformin; the risk can be reduced by avoidance of its prescription in patients with impaired renal function, impaired liver function, cardiac failure, and certain other conditions. Long-term metformin use is associated with decreased vitamin B_{12} levels, and even with biochemical B_{12} deficiency; this complication can detected early by annual assessments of serum B_{12} levels and prevented by annual intramuscular B_{12} administration.

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Introduction

Metformin is a first-line antidiabetic drug. It is a biguanide, belonging to the same class as phenformin. It acts by decreasing intestinal glucose absorption, by decreasing hepatic glucose production, and by increasing insulin sensitivity, among other mechanisms, many of which are only recently being discovered and understood.[1–3] Importantly, metformin use is associated with a low risk of hypoglycemia,[4] making it a safe treatment even in the hands of nonspecialists. Metformin was marketed in the United Kingdom in 1958; in Canada, in 1972; and in the United States, in 1995.[5]

Metformin in Psychiatry

Metformin is emerging as an important option for the prevention or treatment of weight gain, type 2 diabetes mellitus, other elements of the metabolic syndrome, and the metabolic syndrome, itself, in adults and possibly even children who require or receive antipsychotic drugs.[6,7] Psychiatrists who advise metformin therefore need to be aware about important common and uncommon adverse effects of the drug. This article specifically examines gastrointestinal adverse effects of metformin, the risk of lactic acidosis with metformin, and possible vitamin B_{12} deficiency associated with long-term use of metformin.

Gastrointestinal Adverse Effects of Metformin

The gastrointestinal adverse effects of metformin, predominantly nausea, vomiting, abdominal discomfort, flatulence, and diarrhea, are well known; these occur in up to a quarter of treated patients[8] and may lead to up to 5% of patients dropping out of treatment.[9] The risk of these adverse effects can be reduced by gradual dose uptitration, by dosing the medication at mealtimes, and by preferring slow-release formulations over immediate-release formulations.[5]

Metformin and the Risk of Lactic Acidosis

Phenformin, a prototype biguanide, was introduced in the 1950s but was withdrawn from most countries by the late 1970s because of its association with lactic acidosis, a condition characterized by an up to 50% mortality risk.[10] In contrast with phenformin, lactic acidosis is rare with metformin, with estimates of between 3 and 10 cases occurring per 100,000 patient-years. In this context, a pooled analysis of data from 347 comparative trials and cohort studies[11] found no cases of fatal or nonfatal lactic acidosis during 70,490 patient-years of treatment with metformin or during 55,451 patient-years of control treatment. Additionally, there was no difference in mean lactate levels, or difference in change in lactate levels, between metformin and control treatments. The greater safety of metformin relative to phenformin could be due to an inherently lower risk of lactic acidosis or to its conservative labeling, resulting in the reasonably careful avoidance of its prescription for patients in at-risk categories.[10]

Metformin dose-dependently increases plasma lactate levels. However, the increase is clinically insignificant unless metformin levels substantially rise; this can happen in severe renal disease because the

Clinical Points

- Gastrointestinal adverse effects are common with metformin. These include nausea, vomiting, abdominal discomfort, flatulence, and diarrhea. These are less likely to occur with gradual dose uptitration, administration of the drug with meals, and use of a time-release formulation.
- Lactic acidosis is very rare with metformin. The risk can be reduced by avoidance of prescription in patients with significantly impaired renal, liver, or cardiac functioning and patients with certain other risk factors.
- Metformin can impair vitamin B_{12} absorption, and the use of the drug across months to years is associated with a fall in B_{12} levels and even with biochemical B_{12} deficiency. Patients on long-term metformin therapy require annual assessments of serum B_{12} levels. A simpler solution could be preventive management with annual intramuscular B_{12} administration.

drug is eliminated unchanged by the kidneys, and decreased glomerular filtration can result in metformin accumulation. The risk of lactic acidosis is also increased when lactic acid generation is pathologically increased, as in hypoxia due to respiratory or cardiac causes or when lactic acid clearance is pathologically decreased, as in severe liver disease.[10]

Table 1 lists risk factors for metformin-related lactic acidosis. Metformin, however, is often used in even relatively contraindicated populations.[10,12] Readers interested in the use of metformin in restricted categories of patients, especially those with renal insufficiency, are referred to the instructive review of Lipska et al.[12]

Should lactic acidosis arise in the context of metformin treatment, a precipitating medical factor is almost always present. The symptoms of lactic acidosis are nonspecific but develop rapidly; they include rapid, shallow breathing, abdominal discomfort, bowel disturbance, muscle pain, drowsiness, fatigue, weakness, and general malaise. Besides treatment of the precipitating condition, correction of the acidosis is necessary, as well as lowering of metformin levels if drug accumulation is suspected; dialysis is often required. A more detailed discussion on the subject is out of the scope of the present article; interested readers are referred to other reviews.[13,14]

Table 1. Conditions Associated With Increased Risk of Metformin-Related Lactic Acidosis[10,12]

1. Impaired renal functioning due to any cause, including old age. Most countries and guidelines suggest that metformin can be safely used when serum creatinine levels are below 1.5 mg/dL or when the estimated glomerular filtration rate (eGFR) is above 60 mL/min/1.73 m^2, that metformin must be used with caution and at lower doses at eGFR levels between 30 and 60 mL/min/1.73 m^2, and that metformin should be avoided when serum creatinine is above 1.5 mg/dL or eGFR is below 30 mL/min/1.73 m^2.
2. Increased lactic acid production due to any cause, including reduced tissue perfusion associated with dehydration, shock, cardiac failure, or other conditions; hypoxia due to any condition, including respiratory illness; sepsis; or any catastrophic medical condition.
3. Impaired hepatic clearance of lactic acid due to any cause, ranging from hypoperfusion states to frank liver disease.

Notes:
1. Readers are advised to check the metformin label and guidelines that are applicable to their countries of practice.
2. Diabetes, the most important indication for metformin prescription, is itself a risk factor for lactic acidosis. This is because diabetes occurs in older patients, and eGFR falls with increasing age; because diabetes is associated with progressive renal disease; and because lactate levels tend to be higher in diabetic patients. Similarly, other conditions that increase the risk of metformin-associated lactic acidosis may increase the risk through more than 1 pathophysiologic mechanism.

Metformin and Vitamin B_{12}

Metformin impairs the absorption of vitamin B_{12}; however, B_{12} levels may be maintained in the normal range for months to years until the hepatic stores of the vitamin are depleted. Long-term treatment with metformin has been associated with clear evidence of low B_{12} levels, and even of biochemical B_{12} deficiency, as evident from the results of 2 meta-analyses,[15,16] presented below.

Metformin: association with low B_{12} levels. In a systematic review and meta-analysis, Niafar et al[15] identified 18 retrospective cohort studies and 11 randomized controlled trials (RCTs; pooled N = 8,089) that examined B_{12} levels in the context of metformin use.

Metformin treatment, relative to control treatment, was associated with a more than doubled odds of B_{12} deficiency (18 studies; N = 7,611; incidence, 10.7% vs 5.7%; OR, 2.45; 95% CI, 1.74–3.44); heterogeneity was medium (I^2 = 53%), but the risk of publication bias was considered to be low. In an analysis of only the RCTs, metformin use was associated with a nearly doubled odds of B_{12} deficiency (OR, 1.98; 95% CI, 1.46–2.69); this result may be suspect because the forest plot listed 14 RCTs (pooled N = 7,258) whereas, elsewhere in the abstract and text, the authors reported that their systematic review had identified only 11 RCTs. When only RCTs at low risk of bias were analyzed (3 trials), the odds of metformin-associated B_{12} deficiency were more than trebled (OR, 3.41; 95% CI, 1.49–7.84).

In this meta-analysis,[15] an examination of absolute B_{12} levels from 22 studies (pooled N = 4,302) identified lower B_{12} levels, by 65.8 (95% CI, 53.6–78.1) pmol/L, in association with metformin treatment; heterogeneity was high (I^2 = 98%), but the risk of publication bias was considered low. The result narrowly missed statistical significance when only RCT data (10 trials; pooled N = 897) were examined; B_{12} levels were lower in the metformin group by 30.9 (95% CI, −3.7 to 66.7) pmol/L.

The findings remained stable in different sensitivity analyses, including those based on sample size, study design, duration of metformin treatment, definition of B_{12} deficiency, and other variables.[15]

In a more restricted meta-analysis of RCTs that specifically provided change scores, Liu et al[16] identified 6 trials (pooled N = 610 completers) that were 6 to 208 weeks in duration. Serum B_{12} levels were lower with metformin by 37.99 (95% CI, 18.54–57.44) pmol/L in the 4 RCTs (N = 297) that dosed metformin at < 2,000 mg/d and by 78.62 (95% CI, 50.86–106.37) pmol/L in the 2 RCTs (N = 313) that

Table 2. Vitamin B_{12} Level Results With 3 Different CBLAs in 23 Radioisotope Dilution Assay–Defined B_{12} Deficiency Samples[18]

1. Depending on the CBLA method, B_{12} levels were (unexpectedly) found to be in the normal range in 22%, 26%, and 35% of samples.
2. There were 5 (22%) samples in which B_{12} was (wrongly) judged to be in the normal range by all 3 CBLAs.
3. There were 8 samples that were negative for antiintrinsic factor antibodies; in none of these were CBLAs false-normal. There were 15 samples that were positive for antiintrinsic factor antibodies; CBLAs deemed 33%–53% of these to have B_{12} in the normal range. In fact, 9 of these 15 samples were deemed to have normal B_{12} values by at least 1 CBLA.

Abbreviation: CBLA = competitive-binding luminescence assay.

dosed metformin at or above 2,000 mg/d. Thus, there was a dose-dependent effect of metformin in the reduction of B_{12} levels. In other regards, the results of subgroup analyses were similar to those of the overall sample; for example, metformin reduced B_{12} levels regardless of indication (diabetes or polycystic ovarian disease), treatment duration (< 3 years vs 3 years and over), etc.

Clinical importance. Low B_{12} levels are known to be associated with an increased risk of complications that include hyperhomocysteinemia, peripheral neuropathy, megaloblastic anemia, and even psychiatric disorders such as depression and reversible dementia. Because diabetes is the commonest indication for metformin and because diabetes is also associated with peripheral neuropathy, a metformin-associated B_{12} deficiency may not be suspected in metformin-treated diabetic patients with neuropathy; this is a serious clinical concern because peripheral neuropathy occurs earlier during the course of B_{12} deficiency than the anemia and because the neuropathy is largely irreversible. At least 1 study has implicated metformin with neuropathy.[17]

Accuracy of current B_{12} assays. Vitamin B_{12} levels are presently assessed using competitive-binding luminescence assay (CBLA) methods in place of the older microbiologic and radioisotope-dilution assays. In this context, Carmel and Agrawal[18] tested 23 samples of serum using different CBLAs in each of 3 different laboratories. Every sample met criteria for low B_{12} levels as assessed using radioisotope-dilution assay, and all 23 patients had documented pernicious anemia. Important findings of this study are presented in Table 2. In summary, CBLA was associated with an unacceptably high risk of failing to identify low B_{12} levels; however, this risk (33%–53%, depending on the CBLA) occurred only in the presence of antiintrinsic factor antibodies. Whereas positivity for these antibodies is uncommon in the general population, doubts about the accuracy of CBLA for B_{12} assessment have been expressed since at least the year 2000.[18]

Management. Patients receiving long-term treatment with metformin should have annual assessments of B_{12} levels; in fact, this was suggested as early as in the 1970s.[5] However, B_{12} assays are not readily available in all parts of the world, they are expensive, and they may yield false-normal results, as earlier discussed.[18] Furthermore, about 50% of patients with subclinical B_{12} deficiency disease have normal B_{12} levels, and measurement of serum methylmalonic acid and homocysteine, levels of which rise early in vitamin B_{12} deficiency, may be a better way of screening than the measurement of serum B_{12} by itself.[19]

Whereas the intake of daily oral B_{12}-containing supplements may reduce the risk of B_{12} deficiency,[19,20] there is no assurance that this strategy would prove effective, particularly when diabetes is present.[20] Alternately, supplementation with oral calcium may attenuate metformin-associated impairment in B_{12} absorption[21]; however, unless otherwise indicated (as in postmenopausal women), advising calcium supplementation adds to the complexity of the patient's prescription and can result in medication errors and problems in treatment adherence.

In view of these varied and interacting issues related to screening and treatment, the simplest solution could be for all metformin-treated patients to receive an annual intramuscular injection of 1 mg of B_{12}.[5] Such treatment could replenish potentially depleted B_{12} liver stores for the year. B_{12} toxicity is not a concern because excess of the vitamin, if any, would be excreted in urine because the vitamin is water-soluble.

Parting Notes

Most of the data on which this article is based were obtained from studies on the use of metformin for indications such as diabetes. There is no reason to expect that the risks and guidance would be any different in psychiatric populations. Therefore, all the issues outlined in this article must be kept in mind when prescribing metformin in psychiatric contexts.

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