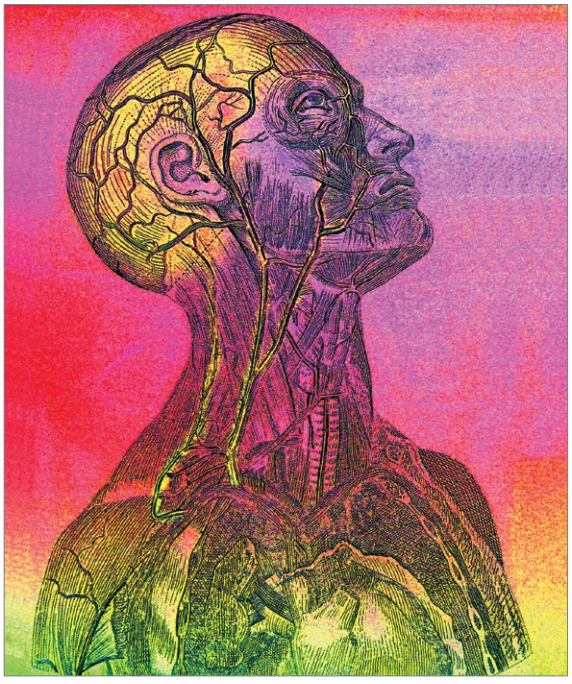
Current PSYCHIATRY

Can anti-inflammatory medications improve symptoms and reduce mortality in schizophrenia?



DENNIS D. POTOKAR/SCIENCE SOURCE

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Research shows that these medications have potential to act as one stone to kill two birds

Consider 3 observations:

- Evidence is mounting that cytokine abnormalities are present in schizophrenia (***Box***[1-8]).
- Reduced arterial compliance (change in volume divided by change in pressure [$\Delta V/\Delta P$] in an artery during the cardiac cycle) is an early marker of cardiovascular disease (CVD) and a robust predictor of mortality, and is associated with cytokine abnormalities.
- People with schizophrenia experience increased mortality from CVD.

Taken together, the 3 statements hint at a hypothesis: *a common inflammatory process involving cytokine imbalance is associated with symptoms of schizophrenia, reduced arterial compliance, and CVD*.

Anti-inflammatory therapeutics that target specific cytokines might both decrease psychiatric symptoms and reduce cardiac mortality in people with schizophrenia. In this article, we (1) highlight the potential role of anti-inflammatory medications in reducing both psychiatric symptoms and cardiac mortality in people with schizophrenia and (2) review the pathophysiological basis of this inflammatory commonality and the evidence for its presence in schizophrenia.

Disclosures
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Box

Several cytokine abnormalities are found in schizophrenia

Evidence of abnormal concentrations of cytokines in people with schizophrenia is robust and revealing:

- In a meta-analysis of 62 studies, people with schizophrenia had increased levels of interleukin (IL)-1 receptor antagonist, soluble IL-2 receptor (sIL-2R), and IL-6; conversely, IL-2 were decreased, relative to controls.[1]
- In another meta-analysis of 40 studies,[2] sIL-2R, IL-12 and tumor necrosis factor-α were trait markers of schizophrenia.
- The serum IL-6 level was significantly higher in 151 participants with schizophrenia compared with 194 controls; a higher concentration of IL-6 correlated positively with greater cognitive impairments.[3]
- An elevated concentration of C-reactive protein (CRP) and exposure to herpes simplex virus type 1 were associated with the severity of cognitive impairments in 588 people with schizophrenia[4]; likewise, in a study of 413 participants with schizophrenia, an elevated concentration of CRP was associated with the severity of cognitive impairments.[5]
- An elevated IL-2 concentration correlated positively with scores on the digit span test of cognitive status in 29 medicated outpatients with schizophrenia.[6]
- In a meta-analysis of 8 studies, the CRP concentration was significantly elevated in people with schizophrenia compared with controls (effect size = 0.45; $P < .001$). In addition, the prevalence of an elevated CRP concentration in people with schizophrenia and a related disorder was 28%.[7]
- In the first study to show an association between an inflammatory biomarker and sensory gating deficit in schizophrenia, 15 of 55 participants (27.3%) with schizophrenia had an elevated CRP concentration that was associated with a higher rate of sensory gating deficit (60% vs 12.5%; $P < .001$), compared with participants with a low CRP concentration.[8]

The 'membrane hypothesis' of schizophrenia

In this hypothesis, a disturbance in the synthesis and structure of membrane phospholipids results in a subsequent disturbance in the function of neuronal membrane proteins, which might be associated with symptoms and mortality in schizophrenia.[9-12] The synaptic vesicle protein synaptophysin, a marker for synaptic density, was found to be decreased in postmortem tissue from the gyrus cinguli in 11 patients with schizophrenia, compared with 13 controls.[10] Intracellular phospholipases A_2 (inPLA$_2$) act as key enzymes in cell membrane repair and remodeling and in neuroplasticity, neurodevelopment, apoptosis, synaptic pruning, neurodegenerative processes, and neuroinflammation.

In a study, people with first-episode schizophrenia (n = 24) who were drug-naïve or off antipsychotic medication were compared with 25 healthy controls using voxel-based morphometry analysis of T_1 high-resolution MRI. inPLA$_2$ activity was increased in the patient group compared with controls; the analysis revealed abnormalities of the frontal and medial temporal cortices, hippocampus, and left-middle and superior temporal gyri in first-episode patients.[11] In another study, inPLA$_2$ activity was increased in 35 people with first-episode schizophrenia, compared with 22 controls, and was associated with symptom severity and outcome after 12 weeks of antipsychotic treatment.[12]

Early CVD mortality in schizophrenia

People with schizophrenia have an elevated rate of CVD compared with the general population; in part, this elevation is linked to magnified risk factors for CVD, including obesity, metabolic syndrome, cigarette smoking, and diabetes[13-17]; furthermore, most antipsychotics can cause or worsen metabolic syndrome.[17]

CVD is one of the most common causes of death among people with schizophrenia.[17,18] Their life expectancy is reported to be 51 to 61 years—20 to 25 years less than what is seen in the general population.[19-21]

Arterial compliance in schizophrenia

Reduced arterial compliance has been found to be a robust predictor of atherosclerosis, stroke, and myocardial infarction[22-29]:

- In 376 subjects who had routine diagnostic coronary angiography associated

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CVD is one of the more common causes of death among people with schizophrenia, who have shortened life expectancy, too

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Anti-inflammatory medications

Clinical Point

Evidence suggests that arterial compliance is increased by anti-inflammatory medications

with coronary stenosis, arterial compliance was reduced significantly—even after controlling for age, sex, smoking, diabetes, hypertension, hyperlipidemia, and obesity.[24]

In a cross-sectional study, 63 male U.S. veterans age 18 to 70 who had a psychiatric diagnosis (16 taking quetiapine, 19 taking risperidone, and 28 treated in the past but off antipsychotics for 2 months) had significantly reduced compliance in thigh- and calf-level arteries than male controls (n = 111), adjusting for body mass index and Framingham Risk Score (FRS). Of the 63 patients, 23 had a diagnosis of schizophrenia or schizoaffective disorder.[30] (The FRS is an estimate of a person's 10-year cardiovascular risk, calculated using age, sex, total cholesterol, high-density lipoprotein, smoker or not, systolic blood pressure, and whether taking an antihypertensive or not. Compliance was measured using computerized plethysmography). Although not statistically significant, secondary analyses from this data set (n = 77, including men for whom factors for metabolic syndrome were available) showed that calf-level compliance (1.82 vs 2.06 mL) and thigh-level compliance (3.6 vs 4.26 mL; P = .06) were reduced in subjects with schizophrenia, compared with those who had another psychiatric diagnosis.[31]

- In another study, arterial compliance was significantly reduced in 10 subjects with schizophrenia, compared with 10 healthy controls.[32]
- Last, reduced total arterial compliance has been shown to be a robust predictor of mortality in older people, compared with reduced local or regional arterial compliance.[33]

Cytokine abnormalities in arterial compliance

The mechanism by which reduced arterial compliance is associated with cardiovascular pathology is not entirely clear. Arterial compliance is a predictor of cardiovascular disorders independent of hypertension.[34] Two studies show that vascular inflammation is associated with reduced arterial compliance.[35,36] Reduced arterial compliance is associated with increased angiotensin II activity; increased nicotinamide adenine dinucleotide phosphate oxidase activity; reduced nitric oxide activity; and increased reactive oxygen species.[37-39] Angiotensin-II signaling activates transforming growth factor-β, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-17, IL-6, and C-reactive protein (CRP)—all of which are associated with reduced arterial compliance.[39-46] In addition, high-sensitivity CRP is significantly associated with reduced arterial compliance.[47-49]

The overlap of cytokine abnormalities linked to schizophrenia and to arterial compliance is depicted in the ***Figure***.

Anti-inflammatory medications and arterial compliance

Evidence suggests that anti-inflammatory medications increase arterial compliance:

- In 10 patients who had coronary artery disease or diabetes, or both, simvastatin (40 mg/d) was administered for 4 months. Arterial compliance improved in all 10 after 2 months of treatment and increased by 34% after 4 months.[27]
- Evidence also suggests that the use of omega-3 fatty acids was associated with increased arterial compliance in people with dyslipidemia.[50]
- Last, in people with rheumatoid arthritis, infliximab, a monoclonal antibody against TNF-α, reduced aortic inflammation; this effect correlated with an increase in aortic compliance.[51]

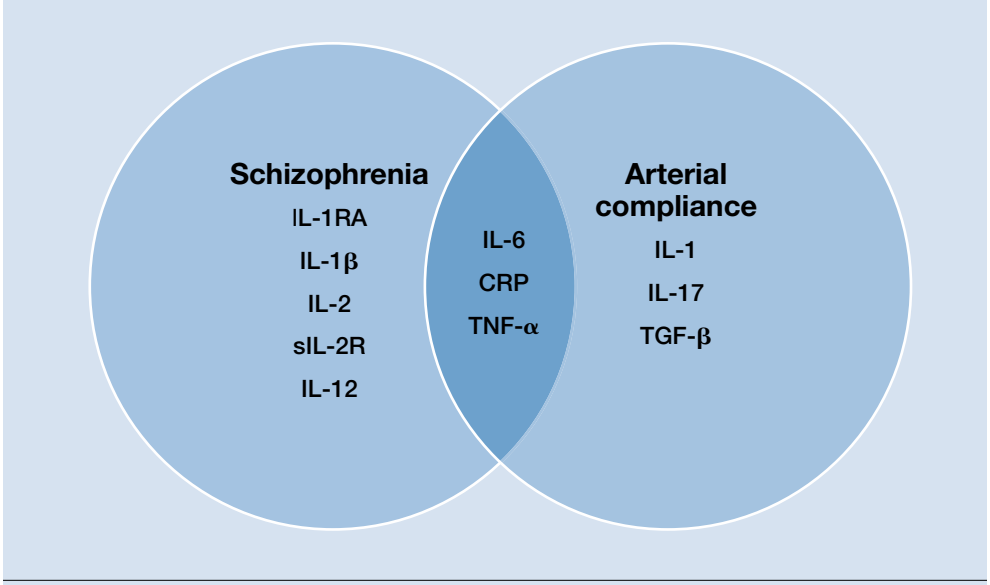
Anti-inflammatory medications in schizophrenia

Two studies have yielded notable findings:

- A meta-analysis of 5 randomized controlled trials (RCTs) involving 264 subjects, comprising 4 studies of celecoxib and 1 of acetylsalicylic acid, had an effect size of 0.43 on total symptom severity. Investigators argued that acetylsalicylic acid might have the additional benefit of decreasing the risk of cardiac death in schizophrenia.[52]
- A review of 26 RCTs examined the efficacy of anti-inflammatory medications on symptom severity in schizophrenia. Acetylsalicylic acid, *N*-acetylcysteine, and

Figure

There is overlap of cytokine abnormalities linked to schizophrenia and to arterial compliance



CRP: C-reactive protein; IL: interleukin; IL-1RA: interleukin receptor antagonist; sIL-2R: soluble IL-2 receptor; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor-α

estrogens had an effect size of 0.3, 0.45, and 0.51, respectively.[53]

Significance of these findings

A revelation that cytokine abnormalities are associated with schizophrenia symptoms and co-occurring somatic illness might offer an important new avenue of therapeutic discovery. On average, people with schizophrenia die 20 to 25 years earlier than the general population; CVD is the major cause of their death. Measuring arterial compliance, a novel noninvasive technology in psychiatry, as well as metabolic parameters, could serve as an early biomarker for assessing risk of CVD.

Implications for psychiatric practice. If inflammation plays a role in CVD in schizophrenia—either independently of factors such as metabolic syndrome, obesity, and smoking, or on the causal pathway linking these factors to reduced arterial compliance and to CVD—treatment with anti-inflammatory medications might reduce the alarming disparity of mortality that accompanies schizophrenia. In short, anti-inflammatory medications may offer a double benefit in this setting. Furthermore, success in this approach could spur clarification of the role of abnormal cytokines in other psychiatric disorders.

At this time, for your patients, consider that anti-inflammatory medications routinely used in medical practice, such as nonsteroidal anti-inflammatory drugs, omega-3 fatty acids, and statins, might alleviate psychiatric symptoms and might reduce cardiovascular mortality in schizophrenia.

Future directions

Perhaps only a limited number of cytokines are common to schizophrenia and reduced arterial compliance. Targeting those specific cytokines might, however, provide the dual benefit in schizophrenia of:

- alleviating symptoms
- reducing the rate of CVD-related mortality.

Studies are warranted to determine the value of (1) anti-inflammatory medications, such as *N*-acetylcysteine and infliximab and (2) anti-inflammatory combination therapy for this dual purpose. In fact, recruit-

Clinical Point

Routinely used anti-inflammatory medications might reduce cardiovascular mortality in your patients who have schizophrenia

Anti-inflammatory medications

Related Resources

- Müller N, Weidinger E, Leitner B, et al. The role of inflammation in schizophrenia. Front Neurosci. 2015;21(9):372. doi: 10.3389/fnins.2015.00372. eCollection 2015.
- Xiong GL, Kenedi, CA. Aspirin to prevent cardiovascular events: Weighing risks and benefits. Current Psychiatry. 2010;9(2):55,56,62,63.

Drug Brand Names

Celecoxib • Celebrex
Infliximab • Remicade
Omega-3 fatty acids • Lovaza
Quetiapine • Seroquel
Simvastatin • Zocor
Risperidone • Risperdal

Clinical Point

Measuring arterial compliance and metabolic parameters might serve as an early biomarker for assessing risk of cardiovascular disease

ment of subjects is underway for a study, Anti-Inflammatory Combination Therapy for the Treatment of Schizophrenia, at the University of Maryland (ClinicalTrials.gov Identifier: NCT01514682).

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Bottom Line

An emerging hypothesis posits a common inflammatory process involving cytokine imbalance that is associated with schizophrenia symptoms, reduced arterial compliance, and cardiovascular disease. Anti-inflammatory medications routinely used in medical practice, such as nonsteroidal anti-inflammatory drugs, omega-3 fatty acids, and statins, might alleviate psychiatric symptoms and reduce cardiac mortality in people with schizophrenia.

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Success in this research approach could spur clarification of the role of abnormal cytokines in other psychiatric disorders