Bilirubin Concentration Correlates With Positive Symptoms in Patients With Schizophrenia

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ABSTRACT

Objective: Besides its toxic effects, bilirubin has been demonstrated to have antioxidant properties to counteract oxidative stress, which has been suggested to play a role in the pathophysiology of schizophrenia.

Methods: This study investigated the potential association between changes in psychopathology measured by the Lindenmayer model of the Positive and Negative Syndrome Scale (PANSS) and changes in total plasma bilirubin concentrations. Data of patients with schizophrenia (*ICD-10*) starting monotherapy with a new-generation antipsychotic were analyzed at baseline (N = 52) and 2 (n = 40), 4 (n = 46), and 12 weeks (n = 30) after the initiation of treatment. Data were collected between December 1997 and October 2007 and analyzed retrospectively.

Results: The PANSS total score decreased significantly from baseline to weeks 2, 4, and 12 of treatment (all *P* values ≤ .001). Total plasma bilirubin concentration also dropped significantly from baseline to week 2 (*P* = .015) and decreased further until week 4 (*P* = .013); no significant decrease was observed between baseline and week 12. Spearman rank correlation revealed a significant association of bilirubin concentration with the PANSS positive ($r = 0.371$, $P = .007$) and excitement ($r = 0.322$, $P = .020$) components at baseline. No further correlations were found. From baseline to weeks 2, 4, and 12, changes in the PANSS positive component correlated significantly with changes in plasma bilirubin concentration (all *P* values < .05), whereas correlations between changes in the remaining PANSS components and bilirubin were less consistent.

Conclusions: Assuming that positive symptoms are associated with the subjective experience of psychological distress, our findings indirectly expand the evidence on potential antioxidant properties of bilirubin in patients with schizophrenia.

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Idiopathic unconjugated hyperbilirubinemia (Gilbert syndrome) was described for the first time in 1901.[1] This mild, persistent disease occurs in about 5% to 10% of white people.[2] In 1905, slight disturbances in liver function, particularly in bilirubin metabolism, were reported for the first time in patients with schizophrenia.[3] In the meantime, a number of studies have confirmed a potential association between hyperbilirubinemia and schizophrenia. Data from Germany and Japan indicate a hyperbilirubinemia prevalence rate of 20% to 25% in these patients, which is significantly higher relative to that of individuals suffering from other psychiatric disorders and the general population.[4,5]

Furthermore, it has been found that schizophrenia patients with elevated plasma bilirubin concentrations may have significantly higher scores on the Positive and General Psychopathology subscales of the Positive and Negative Syndrome Scale (PANSS) compared to patients without hyperbilirubinemia.[5,6] In line with these findings, Yasukawa and colleagues[7] detected an association between a decrease in the concentration of bilirubin oxidative metabolites (biopyrrins) and response to treatment.

Bach et al[8] found increased total bilirubin concentrations in patients suffering from acute and transient psychotic disorders compared to those with paranoid schizophrenia and schizoaffective disorder, but they did not find an association between schizophrenia, in general, and elevated bilirubin concentrations. In contrast, a number of studies have reported on significantly lower plasma antioxidants such as albumin, bilirubin, and uric acid in patients with schizophrenia compared to healthy control subjects.[9–11]

Given these contradictory findings of high and low bilirubin levels in patients with schizophrenia, the relationship between schizophrenia and bilirubin remains unclear. In particular, it is not known whether elevated bilirubin concentrations in schizophrenia patients may be due to environmental or etiologic factors or whether they may simply reflect a more severe stage of the disease. In addition, most of the above-mentioned research is derived from cross-sectional studies.

Using fluid-attenuated inversion-recovery magnetic resonance imaging, Miyaoka et al[12] have demonstrated alterations in the frontotemporal cortex, the limbic system, and the basal ganglia of schizophrenia patients with Gilbert syndrome as compared to those without the syndrome. The authors suggested that, next to other factors, bilirubin may play a substantial role in this regard.[12] Bilirubin itself is usually thought to be a harmful and useless substance in the body, producing subtle encephalopathy in high concentrations.[13]

However, in contrast to this toxic effect, it has also been reported that bilirubin can act as a powerful antioxidant in vitro.[14] Data from the last 2 decades have underscored the antioxidant properties of bilirubin, contributing to defense against increased oxidative stress. Numerous experimental as well as clinical studies have demonstrated an association between low bilirubin concentrations and cardiovascular diseases; diabetes; certain cancers; autoimmune diseases, such as lupus

Clinical Points

- Given the contradictory findings of high and low bilirubin levels in patients with schizophrenia, the relationship between schizophrenia and bilirubin remains unclear.
- The findings of an association between an improvement in positive symptoms and decreased bilirubin concentrations underscore the potential antioxidant effect of bilirubin in schizophrenia patients.

erythematosus or rheumatoid arthritis; or psychiatric disorders, such as schizophrenia.[15–18] Accordingly, a number of antioxidants have been found effective in improving psychotic symptoms.[19,20]

In the current study, prospectively collected antipsychotic drug monitoring data of patients with schizophrenia who were started on monotherapy with a new-generation antipsychotic were analyzed to investigate whether there might be a relationship between psychopathology and bilirubin levels at the beginning and in the course of 3 months of treatment.

METHODS

Subjects and Experimental Design

Patients aged between 18 and 65 years were included in a longitudinal study to build a drug monitoring register at the Medical University of Innsbruck; this is an in-house database for academic research with no public access. Data collected between December 1997 and October 2007 were analyzed retrospectively. Patients met diagnostic criteria for schizophrenia spectrum disorders according to *ICD-10* and signed informed consent forms in accordance with the local ethics committee. They suffered from no other Axis I disorder, including substance abuse. Diagnoses were confirmed using chart information and reports from clinicians who had treated these patients. Patients who had previously been receiving antipsychotic medication underwent a washout period of 3 to 5 days. Patients were excluded if they were taking more than 1 antipsychotic or a long-acting injectable antipsychotic. Antipsychotics were chosen by the psychiatrists treating the patients; dosing followed clinical needs. Total plasma bilirubin concentration and liver enzymes were measured at baseline and after 2, 4, and 12 weeks of treatment. At the same points in time, psychopathology was rated by means of the PANSS.[6] According to Lindenmayer et al,[21,22] this instrument is divided into 5 dimensions: (1) negative component (including the items blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, lack of spontaneity, and active social avoidance), (2) positive component (including the items delusions, hallucinatory behavior, grandiosity, suspiciousness, stereotyped thinking, and unusual thought content), (3) cognitive component (consisting of the items conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, disorientation, and poor attention), (4) excitement component (including the items excitement, hostility, uncooperativeness, and poor impulse control), and (5) depression/anxiety component (consisting of the items anxiety, guilt, tension, and depression). Ratings were completed by psychiatrists belonging to a trained schizophrenia research team. Patients with elevated bilirubin levels at baseline or elevated liver enzymes at any time point were excluded.

Table 1. Patient Characteristics (N = 52)

Characteristic	Value
Age, mean ± SD, y	35.7 ± 10.0
Sex, n (%), male/female	28 (53.8)/24 (46.2)
Duration of illness, mean ± SD, y	8.2 ± 8.1
PANSS score, mean ± SD	
Total score	69.5 ± 17.5
Positive subscale	15.4 ± 5.7
Negative subscale	19.0 ± 6.8
General Psychopathology subscale	35.1 ± 8.7
Antipsychotic treatment, n (%)	
Amisulpride	8 (15.4)
Aripiprazole	4 (7.7)
Clozapine	9 (17.3)
Olanzapine	14 (26.9)
Quetiapine	3 (5.8)
Risperidone	9 (17.3)
Ziprasidone	4 (7.7)
Zotepine	1 (1.9)

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Statistical Methods

All metric variables of interest were checked for normality by means of the Shapiro-Wilk prior to the analysis. As bilirubin concentration and almost all PANSS components showed significant departures from normality for at least 1 assessment time, nonparametric tests were used throughout the analysis. Due to the fairly large proportion of missing observations in the course of time, mainly owing to considerable dropouts after week 4, changes in bilirubin concentration as well as changes in PANSS scores in the time course were tested on a pairwise level by means of the Wilcoxon matched-pairs test (eg, baseline vs week 2, baseline vs week 4). Spearman rank correlation coefficients were used to analyze associations between bilirubin concentration and PANSS scores (PANSS total score and Lindenmayer components); they were also employed to evaluate associations between changes in bilirubin concentration and changes in PANSS scores. All statistical tests were performed at a .05 level of significance.

RESULTS

Demographic and clinical characteristics of the study sample are summarized in Table 1. Data of 52 patients were available for baseline analysis. They had a mean age of approximately 36 years and a mean duration of illness of 8.2 years. Gender distribution was balanced; baseline symptomatology was mild. In terms of the Lindenmayer 5-factor model, negative symptoms showed the highest mean score followed by positive symptoms and depression/anxiety, while the scores regarding cognitive symptoms and excitement were generally low (Table 2). Mean ± SD plasma bilirubin concentration at baseline was 0.627 mg/dL ± 0.263 (see Table 2). All patients started monotherapy with a new-generation antipsychotic.

Table 2. Time Course of Disease Severity (PANSS) and Bilirubin Concentration

Variable	Baseline (N = 52) Mean ± SD	Week 2 (n = 40) Mean ± SD[a]	Week 2 Z^a	Week 2 P^a	Week 4 (n = 46) Mean ± SD[a]	Week 4 Z^a	Week 4 P^a	Week 12 (n = 30) Mean ± SD[a]	Week 12 Z^a	Week 12 P^a
PANSS										
Total score	69.5 ± 17.5	59.3** ± 19.8	−4.2	< .001	60.3** ± 19.1	−4.4	< .001	54.8** ± 19.4	−3.2	.001
Positive subscale	15.4 ± 5.7	12.1** ± 4.3	−4.0	< .001	12.0** ± 4.9	−4.5	< .001	10.4** ± 3.1	−2.9	.004
Negative subscale	19.0 ± 6.8	17.7* ± 7.9	−2.4	.017	17.7* ± 7.2	−2.5	.012	17.0 ± 8.7	−1.9	.063
General Psychopathology subscale	35.1 ± 8.7	29.5** ± 9.8	−4.0	< .001	30.6** ± 9.3	−4.1	< .001	27.4** ± 9.8	−3.3	< .001
Negative component[b]	2.79 ± 1.07	2.53** ± 1.21	−2.8	.006	2.66 ± 1.11	−1.1	NS	2.53 ± 1.22	−1.7	.098
Positive component[b]	2.54 ± 1.00	2.05** ± 0.90	−3.8	< .001	1.95** ± 0.87	−4.6	< .001	1.67** ± 0.62	−3.1	.002
Cognitive component[b]	2.08 ± 0.79	1.72** ± 0.65	−3.9	< .001	1.73** ± 0.70	−3.7	< .001	1.62* ± 0.61	−2.3	.023
Excitement component[b]	1.41 ± 0.56	1.19* ± 9.8	−2.0	.046	1.20** ± 0.32	−3.0	.002	1.18 ± 0.31	−0.8	NS
Depression/anxiety component[b]	2.40 ± 0.79	2.03** ± 9.8	−3.7	< .001	2.27 ± 0.82	−1.4	NS	1.80** ± 0.84	−3.3	< .001
Plasma bilirubin level (mg/dL)	0.627 ± 0.263	0.548* ± 0.222	−2.4	.015	0.515* ± 0.248	−2.5	.013	0.563 ± 0.233	−1.0	NS

[a]Comparison with baseline scores by means of the Wilcoxon matched-pairs test. No significant differences for any other pairs of assessment times (week 2 vs week 4, week 4 vs week 12, week 2 vs week 12).
[b]PANSS components were defined according to the Lindenmayer 5-factor model[21,22] and scored on a 1 (no symptom) to 7 (extremely severe symptom) scale.
*Significantly lower than at baseline, $P < .05$ (Wilcoxon test).
**Significantly lower than at baseline, $P < .01$ (Wilcoxon test).
Abbreviations: NS = not significant ($P > .1$), PANSS = Positive and Negative Syndrome Scale.

Table 3. Association of Psychopathology (PANSS components[a]) With Bilirubin Concentration at Baseline[b]

PANSS Component	Spearman Rank Correlation With Bilirubin Concentration: *r* Spearman	*P* Value
Negative	−0.146	.303
Positive	0.371*	.007
Cognitive	0.065	.648
Excitement	0.322*	.020
Depression/anxiety	0.018	.903

[a]PANSS components were defined according to the Lindenmayer 5-factor model[21,22] and scored on a 1 (no symptom) to 7 (extremely severe symptom) scale.
[b]No significant correlation of PANSS factors with plasma bilirubin concentration at any other time point (weeks 2, 4, and 12 of treatment).
*$P < .05$.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 4. Association of Change in Psychopathology (PANSS components[a]) With Change in Bilirubin Concentration

Change in Psychopathology (PANSS)	Change in Bilirubin Concentration[b] [*r* (*P* value)]: Week 0–Week 2	Week 0–Week 4	Week 0–Week 12
Negative	0.065 (NS)	−0.196 (NS)	0.089 (NS)
Positive	**0.479 (.002)**	**0.438 (.002)**	**0.434 (.017)**
Cognitive	0.060 (NS)	**0.345 (.019)**	**0.405 (.027)**
Excitement	**0.495 (.001)**	**0.355 (.015)**	0.312 (.093)
Depression/anxiety	0.165 (NS)	−0.073 (NS)	0.170 (NS)
Total score	**0.336 (.034)**	0.251 (.092)	**0.373 (.042)**

[a]PANSS components were defined according to the Lindenmayer 5-factor model[21,22] and scored on a 1 (no symptom) to 7 (extremely severe symptom) scale.
[b]Spearman rank correlation (*P* value in parentheses). Bold indicates statistical significance.
Abbreviations: NS = not significant, PANSS = Positive and Negative Syndrome Scale.

Data of 40 patients were available for analysis at week 2, of 46 patients at week 4, and of 30 patients at week 12. The time course of disease severity and mean plasma bilirubin concentration is shown in Table 2. The PANSS total score improved significantly from baseline to week 2, week 4, and week 12 ($P \leq .001$, each). Regarding the Lindenmayer 5-factor model, the positive and cognitive components were significantly lower at week 2, week 4, and week 12 compared to baseline, whereas the excitement component decreased significantly from baseline to week 2 and week 4, but not from baseline to week 12. The negative component improved significantly from baseline to week 2, however, at week 4 and week 12, no significant improvement from baseline was observed. Lastly, the depression/anxiety component improved significantly from baseline to week 2 and week 12, but not from baseline to week 4. Mean plasma bilirubin concentration dropped significantly from baseline to week 2 and week 4, and slightly increased again thereafter (without attaining statistical significance).

Regarding the simultaneous assessments of psychopathology and plasma bilirubin concentration, both positive symptoms and excitement were positively associated with baseline plasma bilirubin concentration (Table 3). There was no further correlation between psychopathology and plasma bilirubin concentration, neither at baseline nor at any other time point.

The association of changes in psychopathology with changes in plasma bilirubin concentration is depicted in Table 4. Changes of the PANSS total score from baseline were significantly associated with changes in bilirubin concentration at week 2 and week 12, but did not reach statistical significance at week 4. Correlation analyses including all 5 components of the PANSS revealed that changes in the positive component showed the strongest association with plasma bilirubin concentration, ie, an amelioration of positive symptoms from baseline to week 2, week 4, and week 12, respectively, went along with lower plasma bilirubin concentration. Changes of cognitive symptoms from baseline correlated significantly with changes in bilirubin concentration at week 4 and week 12, but not at week 2. In addition, changes in the excitement component from baseline correlated significantly with changes in bilirubin concentration at week 2 and week 4. We found no significant correlation between changes in both the negative and depression/anxiety components from baseline and changes in bilirubin concentration at any assessment time.

DISCUSSION

In the current study, schizophrenia patients starting monotherapy with a new-generation antipsychotic were prospectively followed up for 3 months to investigate a potential correlation between changes in psychopathology and bilirubin concentration. As expected, psychopathological symptoms improved over the course of treatment. Mean baseline plasma bilirubin concentration was comparable to that of the healthy adult US population[23] and dropped significantly from baseline to weeks 2 and 4 of treatment, whereas the decline from baseline to week 12 was not significant. Notably, during the first 2 weeks of antipsychotic treatment, the amelioration of psychopathological symptoms correlated significantly ($P = .034$) with the decrease in bilirubin concentration; and even after 12 weeks of treatment, the correlation between changes in bilirubin concentration and positive symptoms from baseline was significant.

By including solely patients whose plasma bilirubin concentration was within the normal range at baseline, we were able to exclude hyperbilirubinemia caused by other factors such as Gilbert syndrome, fasting, or medication. Generally, psychopharmacologic treatment can raise bilirubin levels by non–dose-related allergic reactions or dose-related minor abnormalities in liver function.[24] However, previous reports on a potential association between schizophrenia and hyperbilirubinemia identified that antipsychotics lowered bilirubin levels rather than raised them.[4,5] Accordingly, our finding of a decreasing bilirubin concentration over the course of antipsychotic treatment is in line with that of Yasukawa et al.[7] However, that study did not determine total bilirubin but its oxidative metabolites (biopyrrins) in urine. Furthermore, the authors reported on biopyrrin levels during acute (first admission to the hospital), subacute (1 month after admission), and remission states (on discharge) of a relatively small patient sample without using a formal instrument to describe changes in symptomatology more precisely.

Generally, oxidative damage to lipids, proteins, and DNA is known to impair cell viability and function. Bilirubin has been demonstrated to have antioxidant properties and to counteract oxidative stress, which has been suggested to be intimately linked to a variety of pathophysiologic processes, such as inflammation, oligodendrocyte abnormalities, and mitochondrial dysfunction.[25] At micromolar concentrations in vitro, bilirubin is able to efficiently scavenge peroxyl radicals.[14] Furthermore, under 2% oxygen, it suppresses the oxidation in liposomes more than α-tocopherol, which is regarded as the best antioxidant of lipid peroxidation.[14] The plasma total antioxidant status, which encompasses the antioxidant agents uric acid, albumin, and bilirubin, has been demonstrated to be lower in patients with schizophrenia than in healthy individuals.[10] Moreover, the total antioxidant status is inversely correlated with symptom severity during the drug-free condition, thus strengthening the evidence for an antioxidant defense deficit in schizophrenia.[10]

Yamaguchi et al[26] investigated the link between psychological stress and oxidative stress in healthy volunteers and found increased bilirubin metabolites in human urine after having been exposed to stress. Given these findings and the consistent correlation of changes in total plasma bilirubin concentration with changes in the PANSS positive component in the current study, we suggest that positive symptoms may be more likely to be associated with the subjective experience of psychological distress in schizophrenia patients than other symptoms (eg, negative or cognitive symptoms).

However, when interpreting our data, one has to consider several limitations of our study. Patient diagnoses were obtained through chart review and clinical conversation and were not rigorously diagnosed with a formal instrument. Additionally, that interrater reliability was not assessed over the course of this study is a major limitation, although the research team members regularly participated in PANSS rater trainings. The mean PANSS subscores in our patient sample are rather low. A higher degree of symptomatology may have led to different findings, and accordingly, our results have to be seen with caution. Furthermore, that the number of subjects studied during the course of the trial fluctuated because some patients withdrew consent or simply missed the assessment time during outpatient treatment clearly limits the generalizability of our data.

To summarize, we found a consistent correlation of changes in the Lindenmayer PANSS positive component and changes in bilirubin concentration over the course of treatment, whereas changes in the PANSS total scores as well as the excitement and cognitive components correlated less consistently with changes in bilirubin concentration. Changes in negative and affective symptomatology did not correlate with plasma bilirubin concentration. In line with the previously mentioned considerations regarding a possible link between psychological distress and increased bilirubin metabolites, we suggest that positive symptoms are more likely to be associated with the subjective experience of psychological distress in schizophrenia patients.[22] The consistent correlation of changes in the PANSS positive component with changes in plasma bilirubin levels expands the evidence on potential antioxidant properties of bilirubin in schizophrenia patients, particularly caused by the stress of positive symptoms. However, we did not prospectively address this issue, and future studies with larger sample sizes are needed to confirm this hypothesis.

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REFERENCES

1. Gilbert A, Lereboullet P. La cholemie simple familial. *Semaine Med*. 1901;21:241–245.
2. Bosma PJ. Inherited disorders of bilirubin metabolism. *J Hepatol*. 2003;38(1):107–117.
3. Trapsad L. Étude des troubles physique dans la démence précoce hébéphréno-catatonique [Thèse]. Paris, France: 1905.
4. Müller N, Schiller P, Ackenheil M. Coincidence of schizophrenia and hyperbilirubinemia. *Pharmacopsychiatry*. 1991;24(6):225–228.
5. Miyaoka T, Seno H, Itoga M, et al. Schizophrenia-associated idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *J Clin Psychiatry*. 2000;61(11):868–871.
6. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
7. Yasukawa R, Miyaoka T, Yasuda H, et al. Increased urinary excretion of biopyrrins, oxidative metabolites of bilirubin, in patients with schizophrenia. *Psychiatry Res*. 2007;153(2):203–207.
8. Bach DR, Kindler J, Strik WK. Elevated bilirubin in acute and transient psychotic disorder. *Pharmacopsychiatry*. 2010;43(1):12–16.
9. Yao JK, Reddy R, McElhinny LG, et al. Reduced status of plasma total antioxidant capacity in schizophrenia. *Schizophr Res*. 1998;32(1):1–8.
10. Yao JK, Reddy R, van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. *Psychiatry Res*. 2000;97(2–3):137–151.
11. Pae CU, Paik IH, Lee C, et al. Decreased plasma antioxidants in schizophrenia. *Neuropsychobiology*. 2004;50(1):54–56.
12. Miyaoka T, Yasukawa R, Mihara T, et al. Fluid-attenuated inversion-recovery MR imaging in schizophrenia-associated with idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *Eur Psychiatry*. 2005;20(4):327–331.
13. Shapiro SM. Definition of the clinical spectrum of kernicterus and bilirubin-induced neurologic dysfunction (BIND). *J Perinatol*. 2005;25(1):54–59.
14. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. *Science*. 1987;235(4792):1043–1046.
15. Sedlak TW, Snyder SH. Bilirubin benefits: cellular protection by a biliverdin reductase antioxidant cycle. *Pediatrics*. 2004;113(6):1776–1782.
16. Vítek L. Impact of serum bilirubin on human diseases. *Pediatrics*. 2005;115(5):1411–1412.
17. Vítek L. The role of bilirubin in diabetes, metabolic syndrome, and cardiovascular diseases. *Front Pharmacol*. 2012;3:55.
18. Vítek L. Relationship of bilirubin to diseases caused by increased oxidative stress [article in Czech]. *Vnitr Lek*. 2013;59(7):618–621.
19. Miyamoto S, Miyake N, Jarskog LF, et al. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Mol Psychiatry*. 2012;17(12):1206–1227.
20. Miyamoto S, Jarskog LF, Fleischhacker WW. Alternative pharmacologic targets for the treatment of schizophrenia: results from phase I and II trials. *Curr Opin Psychiatry*. 2013;26(2):158–165.
21. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. Five-factor model of schizophrenia. initial validation. *J Nerv Ment Dis*. 1994;182(11):631–638.
22. Lindenmayer JP, Grochowski S, Hyman RB. Five factor model of schizophrenia: replication across samples. *Schizophr Res*. 1995;14(3):229–234.
23. Zucker SD, Horn PS, Sherman KE. Serum bilirubin levels in the US population: gender effect and inverse correlation with colorectal cancer. *Hepatology*. 2004;40(4):827–835.
24. Dincsoy HP, Saelinger DA. Haloperidol-induced chronic cholestatic liver disease. *Gastroenterology*. 1982;83(3):694–700.
25. Bitanihirwe BK, Woo TU. Oxidative stress in schizophrenia: an integrated approach. *Neurosci Biobehav Rev*. 2011;35(3):878–893.
26. Yamaguchi T, Shioji I, Sugimoto A, et al. Psychological stress increases bilirubin metabolites in human urine. *Biochem Biophys Res Commun*. 2002;293(1):517–520.