# Psychiatric drug-nutrient interactions of vitamin D: a retrospective study

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## INTRODUCTION

**Background**

- Vitamin D is an essential micronutrient that regulates calcium and phosphate concentrations.[1] Cholecalciferol (parent vitamin D3), which is obtained from the sunlight-mediated biosynthesis or diet, is converted to 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] through cytochrome P450 (CYP) mediated hydroxylation. 1,25(OH)2D3 (calcitriol) is the active form of vitamin D3 which is known to regulate calcium concentrations when it falls below normal levels. Calcitriol also regulates components of immune system and parathyroid hormone levels.[2] Interestingly, calcitriol is inactivated through hydroxylation reactions which is primarily catalyzed by CYP3A4 enzyme in the liver.[2] Low vitamin D levels have been linked to chronic psychiatric conditions including depression and acute episodes of schizophrenia.[3,4]

**Purpose**

- There are limited data regarding interactions between vitamin D derivative and psychiatric drugs (i.e., antidepressants, antipsychotics, anticonvulsants). Multiple psychiatric drugs can either induce or inhibit hepatic CYP3A4 functions, leading to possible altered levels of calcitriol. We hypothesize that patients on psychiatric medications (e.g., antidepressants, antipsychotics, anticonvulsants) will have altered vitamin D levels due to plausible drug-nutrient interactions.

## METHODS

**Evaluate retrospective vitamin D levels in patients on psychiatric medications**

Data Collection

- Patient medical records will be observed from March 2020 to June 2021
- Patient information will be deidentified by using random identification number (e.g., 100A, 101B, 102C, 103D)
- Figure 1 was derived observing how many psychiatric medications the included patients were taking and comparing it to their vitamin D level.

Inclusion Criteria

- Adults ≥ 18 years old
- At least one vitamin D level measured prior to index admission
- At least two laboratory results of vitamin D during index admission
- At least one prescribed psychiatric drug (i.e., antidepressant, antipsychotic, or anticonvulsant) since March 2020 and continued for at least three months

Psychiatric medications

- Defined as drugs with CYP3A4 involvement through CYP substrate metabolism, inhibition, and induction
- Classes of psychiatric medications include Selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCA), heterocyclics, monoamine oxidase inhibitors (MAOI), atypical antipsychotics, typical antipsychotics, mood stabilizing agents, and anxiolytics

**Simulate in silico CYP-related interactions between psychiatric medications and vitamin D.**

In Silco Data Analysis

- GastroPlus version 9.8 is a simulation software that can estimate the properties of pharmacokinetics, pharmacodynamics, and simulate drug-drug interactions
- GastroPlus modules ADMET Predictor, PBPK, and DDI were used in the analysis
- ADMET Predictor module determined
- PBPK modeling used for the DDI simulation was a 30-year-old, white male, weight 85 kg, and BMI 27
- DDI modelling for calcitriol and included psychiatric medications was conducted using steady-state simulation in GastroPlus

## RESULTS

**Figure 1: Correlational between number of psychiatric medications taken and vitamin D level**

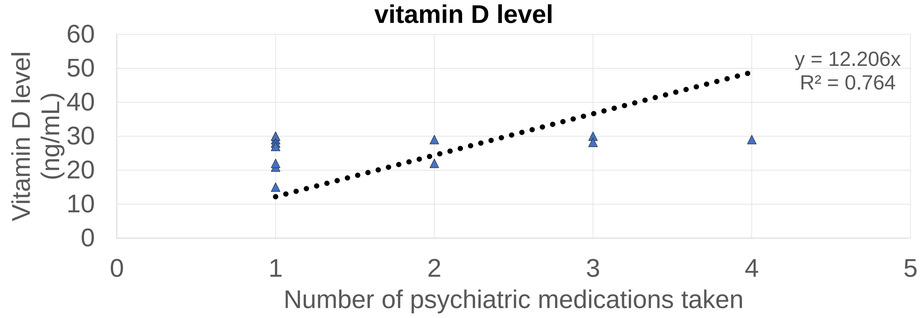


**Figure 2: Structure of Calcitriol (1,25-dihydroxyvitamin D3)**

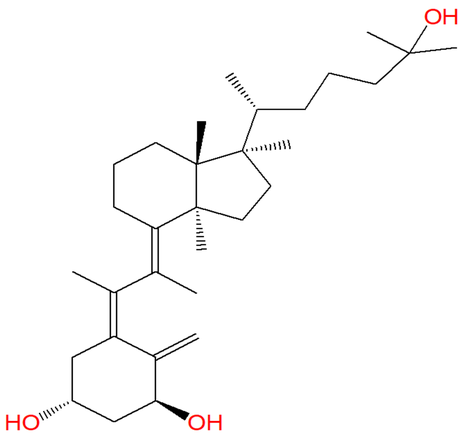


**Table 1: Involvement of CYP enzymes in the metabolism of psychiatric medications and their CYP inhibitory properties**

| Psychiatric Medications | CYP substrate | CYP inhibition/Ki values (μM) | CYP induction/EC50 value (μM) |
|---|---|---|---|
| **Typical Antipsychotics** | | | |
| Haloperidol | CYP1A2, CYP2D6, CYP3A4 | CYP3A4 (Ki: 1.38) | N/A |
| **Atypical Antipsychotics** | | | |
| Risperidone | CYP2D6, CYP3A4 | CYP3A4 (Ki: 10.35) | N/A |
| Olanzapine | CYP1A2, CYP2D6 | CYP3A4 (Ki: 21.10) | N/A |
| **SSRI Antidepressants** | | | |
| Fluoxetine | CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP2E1, CYP3A4 | CYP3A4 (Ki: 8) | N/A |
| Fluvoxamine | CYP1A2, CYP2D6 | CYP3A4 (Ki: 24) | N/A |
| **Anticonvulsants** | | | |
| Carbamazepine | CYP2C8, CYP3A4 | N/A | CYP3A4 (EC50: 59) |
| Phenytoin | CYP2C19, CYP2C9, CYP3A4 | N/A | CYP3A4 (EC50: 24) |

**Table 2: GastroPlus Simulated Drug-Drug Interaction**

| Victim Drug | Perpetrator Drug | Drug- Drug Interaction Outcome |
|---|---|---|
| Calcitriol | Haloperidol | No interaction |
| | Risperidone | No interaction |
| | Olanzapine | No interaction |
| | Fluoxetine | No interaction |
| | Fluvoxamine | No interaction |
| | Carbamazepine | Strong interaction |
| | Phenytoin | Moderate interaction |

## DISCUSSION AND CONCLUSION

- Calcitriol ADMET Predictor properties indicate its fraction metabolized mainly by CYP3A4 and has a high blood brain barrier penetration.
- From literature review we determined the in vitro Ki and EC50 values for haloperidol, risperidone, olanzapine, fluoxetine, fluvoxamine, carbamazepine, and phenytoin CYP3A4 involvement. However, the DDI simulation only yielded an interaction with carbamazepine and phenytoin. It is not expected that haloperidol, risperidone, olanzapine, fluoxetine, and fluvoxamine have any interaction with altering calcitriol.
- Limitations of the study include the lack hospital data due to COVID-19. We are still proceeding the vitamin D levels in patient on psychiatric medications. We plan to present risk ratios and correlations of the data when completed and provide a follow-up to the study.

## REFERENCES

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## DISCLOSURES

- Research is sponsored by a CPNP Foundation Defining the Future Grant
- GastroPlus software 9.8 version was provided by Simulations Plus Inc. (Lancaster, CA)