Nutrient Drug Interaction Probability Scale (NDIPS): An External Validation

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BACKGROUND

A Drug-Nutrient Interaction (DNI) is any type of physical, chemical, physiologic or pathophysiologic interaction between a drug and a nutrient.

The relationship can be confounded by:
- The route of administration,
- Health status of the patient,
- Nutritional status of the patient,
- End-organ function or excretion routes,
- Environmental factors,
- and even genetics.

This complicated relation is the basis of DNI research.

Set of two-way interactions:
- Drugs can affect nutritional status
- Nutrients can influence drug behavior and concentration

Drug-*food* interaction ≠ DNI
- A drug-*nutrient* interaction should be focused on a specific nutrient.

The recently published FDA guidelines do not consider DNIs during the drug development phase.

JUSTIFICATION

A clinical tool adapted for the healthcare practitioner to assess for the probability of DNIs is an urgent and unmet need.

PROJECT AIMS

1. Develop a screening tool to assess the probability of DNIs.
2. Conduct an internal validation process using published evidence across the literature to evaluate the accuracy of the tool.
3. Perform a clinical test drive that measures consistency in question interpretation and clarity with the assistance of practicing clinicians.

NDIPS Basic Design:

- To be applied in clinical scenarios where there is a raised suspicion or concern of DNI.
- Meant to serve as a thought process for the clinician when assessing DNIs.
- Designates either positive, negative, or neutral points that will be added to then determine the probability.

Questionnaire content:

1. Proposed **mechanism of interaction**
2. Documented **case reports/case series**
3. Presence of **subjective evidence**
4. Presence of **objective evidence**
5. Presentation within **reasonable time frame**
6. Remission of interaction upon **changes in drug regimen** with no changes in nutrient intake
7. Remission of interaction upon **changes in nutrient intake** with no changes in drug regimen
8. **Alternative causes** for the event
9. Underlying **nutrient alterations**
10. Underlying **diagnoses or current illness**

Final product:

Questions	Yes	No	Unk/NA
1. Is there a **proposed mechanism of interaction** for the specific drug nutrient combination under review?	+1	-1	0
2. Are there previous **documented case reports or case series** of this interaction in humans?	+1	-1	0
3. Is there **subjective evidence** in the patient that supports the interaction between the drug and nutrient under review? Explanation: **Are there any signs/symptoms** consistent with the effects of the DNI under review?	+1	-1	0
4. Can the interaction be confirmed by any **objective evidence** presented by the patient consistent with the proposed mechanism of interaction? Explanation: Are there any **laboratory results, imaging results or additional information** relevant to the DNI under study?	+1	-1	0
5. Does the objective/subjective evidence presented in the patient follow a **reasonable timeframe** according to the proposed mechanism of interaction?* For example: B12 depletion takes months to develop following the administration of specific medications (proton pump inhibitors[2,3])	+1	-1	0
6. If you answered "Yes" in either questions 3 and/or 4, are the events associated with a **dechallenge or changes in dose of the drug** with **no changes in nutrient support/intake**? Explanation: Did signs and symptoms remit with changes in dosage of drug without any changes in the dietary pattern of administration of the specific nutrient under review?	+1	-1	0
7. If you answered "Yes" in either questions 3 and/or 4, are the events associated with **changes in the specific nutrient regimen under review** with no dechallenge in the administration or dosage of the drug? Explanation: Is NPO or other type of dietary change without any changes in drug administration associated with decrease of signs/symptoms?	+1	-1	0
8. Are there reasonable **alternative causes** for the event?**	-1	+1	0
9. Is there a strong reason to believe that the patient's presentation is more related to **underlying nutrient alterations**, rather than a drug-nutrient interaction? For example: nutrition-related anemia.	-1	+1	0
10. Is there a strong reason to believe that the patient's presentation is more related to the **underlying diagnoses or current illness**, rather than a drug-nutrient interaction? For example, malabsorption disorders, the patient is critically ill, underlying intestinal dysfunction, fistulas, bacteremia, etcetera.	-1	+1	0

NDIPS result interpretation:
Highly Probable: >8; Probable: 5-8; Possible: 2-4; Doubtful: <2

RESULTS: Internal Validation

Methods: input a variety of case reports describing DNIs to simulate real-life clinical scenarios.

Figure No. 1: Plot line of cumulative NDIPS trajectory by individual DNI pairs

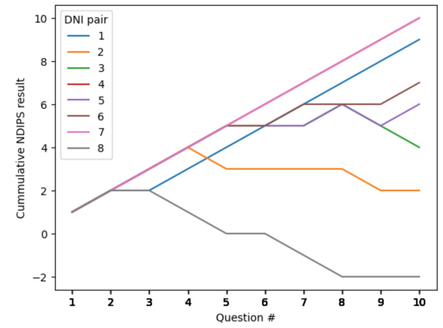
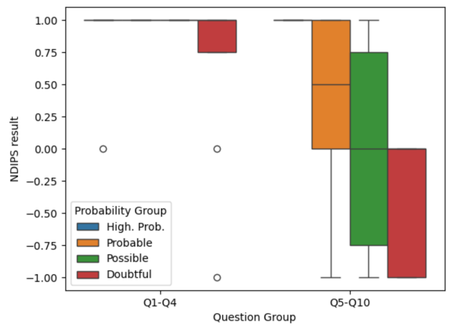


Figure No. 2: Boxplot of NDIPS results stratified by both probability groups and question category



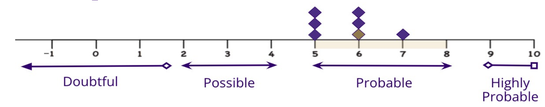
Implications of findings:

1. The **current method** for assessing and managing interactions is **not necessarily associated with a high probability** of DNIs.
2. The current method lacks **personalization** according to each clinical presentation.
3. Unnecessary **treatment adaptations** are imminent, and they will continue to happen until we have a **more accurate and personalized model.**

RESULTS: External Validation

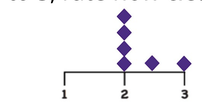
Methods: clinicians fill out the NDIPS using a selected case report and complete a feedback survey.
- Based on preliminary feedback, methods shifted to accommodate a more controlled environment.

a) Clinicians' probability results from case report:



b) Survey content:

On a scale of 1 to 3, rate how clearly the questions are stated.



c) Summary of findings:

- Clinicians interpret questions the same way.
- Questions 1 and 2 should be neutral and serve as thought process, but not affect the result.
- Questions 8, 9, and 10 seem repetitive and could be a single question.
- A shorter survey would be more practical and usable for real life-scenarios.
- The language is perceived as complex, incorporate a concise and user-friendly vocabulary.

Future directions:

1. Incorporate feedback received on the areas for improvement to the tool.
2. Perform additional sets of external validations until feedback indicates that the tool is ready for the next phase, which is clinical applicability in real-life scenarios.
3. Extend sample size to include other practicing clinicians, additional to dietitians.

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