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**One Sentence Summary:** No more than 40 characters.

**Abstract:** 125 words or less.

**Main Text:**

**References and Notes:** (Followed by a numbered list); only a single reference list should be provided for the main text and supplemental information.

**Acknowledgments:** Split into sections as described below.

**List of Supplementary Materials:** Include a list, noting which references are only cited in the SM.

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**Supplementary Materials:** Comprising Materials and Methods, figures, and tables; should be in a separate file.

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Drugs synergistically affect adverse outcomes through protein-protein interaction networks

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**Abstract:** A traditional viewpoint on drug interactions emphasizes competitive binding of multiple drugs with a shared protein target. However, drug-binding proteins exist within protein-protein interaction networks within the cell, suggesting that adverse outcomes could result from long-range network effects. Here we investigated whether combinations of drugs could affect severe adverse outcomes if the drug’s binding proteins were known to interact through protein-protein interaction networks. We first predicted drug-drug-adverse-outcome relationships using an interaction network analysis and validated these predictions using an observational study in the clinical record. These results demonstrate a novel paradigm for considering adverse outcomes from drug combinations that do not arise from competitive binding at a shared protein target.

The abstract should be 100-125 words, and organized in this structure: An opening sentence that sets the question that you address and is comprehensible to the general reader, background content specific to this study, results, and a concluding sentence. It should be a single paragraph.

**One Sentence Summary:** Protein-protein interactions of drug targets can mediate severe adverse outcomes of drug combinations.

**Main Text:** In general, this should include a brief (1-2 paragraph) introduction, followed by a statement of the specific scope of the study, followed by results and then interpretations. Please avoid statements of future work or claims of priority, and avoid repeating the conclusions at the end.

**Subheadings** (“Results”, “Discussion”, or more specific subheadings, but not a leading “Introduction”) may be included in Research Articles or Reviews and should be brief, set off by a line break and formatted in bold face. Reports should not have subheadings.

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Supplementary Materials:

Materials and Methods

Figures S1-S#

Tables S1-S#

Movies S1-S#

Audio Files S1-S#

External Databases S1-S#

References (*##-##*)

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