'Imperfect drug penetration' speeds pathogens' resistance, study finds

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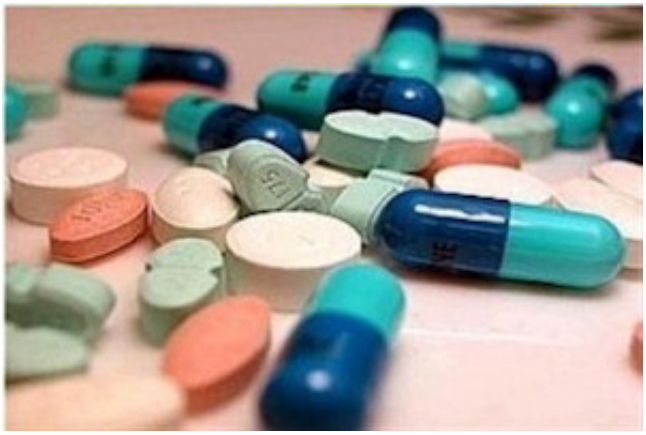

Various pills. Credit: Wikipedia

Prescribing patients two or more drugs that do not reach the same parts of the body could accelerate a pathogen's resistance to all of the drugs being used in treatment, according to a new study published today in the *Proceedings of the National Academy of Sciences*.

Not all drugs can reach all parts of the body, a situation known as "imperfect drug penetration." In the study, researchers found that when there is a "pocket" of the body where only one drug is present, such as the brain or the digestive system, a pathogen can quickly develop resistance to one drug at a time.

"If there is a space where there is only one drug, that's the place where the pathogen can start its escape," said Pleuni Pennings, an assistant professor of biology at San Francisco State University and coauthor of the study. "Once it no longer has the first drug to deal with, it's very easy for it to quickly become resistant to a second drug."

The study could have major implications for how treatment plans are designed and prescribed to patients of HIV, malaria, tuberculosis and other ailments. Because pathogens can quickly develop resistance to a single drug, providers often prescribe multiple drugs to increase their effectiveness.

The results of the study suggest that, when doing so, doctors should carefully consider which parts of the body each drug will reach and whether selecting medications with imperfect but similar penetrations might be the best treatment option.

"It may be better in some cases to leave a pocket of the body without any drugs instead of leaving a pocket with just one drug," Pennings said.

The study is the first to look at the connection between drug penetration and multidrug resistance. Pennings and her colleagues ran computer simulations to look at the behavior of pathogens such as viruses or bacteria in response to changes in the drugs used in treatment and their levels of penetration. They found that, in instances where even small parts of the body could only be reached by one drug, the pathogen's ability to build resistance to both drugs accelerated compared to situations where no such pockets existed.

"This requires a new way of thinking about drug combinations that is a bit counterintuitive," Pennings said. "Suppose that drug A does not reach the brain, but drug B does. You'll see the pathogen evolving resistance to drug B and assume that's where the problem lies. But in fact it is drug A that is not doing its job because it's not reaching the brain, and that's the drug you may have to actually fix."

Future research will begin to outline the most effective drug combinations by exploring which parts of the body cannot be reached by specific drugs and where and how quickly specific pathogens are able to develop resistance.

More information: "Imperfect drug penetration

leads to spatial monotherapy and rapid evolution of multidrug resistance" by Stefany Moreno-Gamez, Alison L. Hill, Daniel I. S. Rosenbloom, Dmitri A. Petrov, Martin A. Nowak and Pleuni S. Pennings was published May 18 in the *Proceedings of the National Academy of Sciences*: www.pnas.org/content/early/2015/05/15/1424184112

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