SJM Commentary

"No Better than Placebo"

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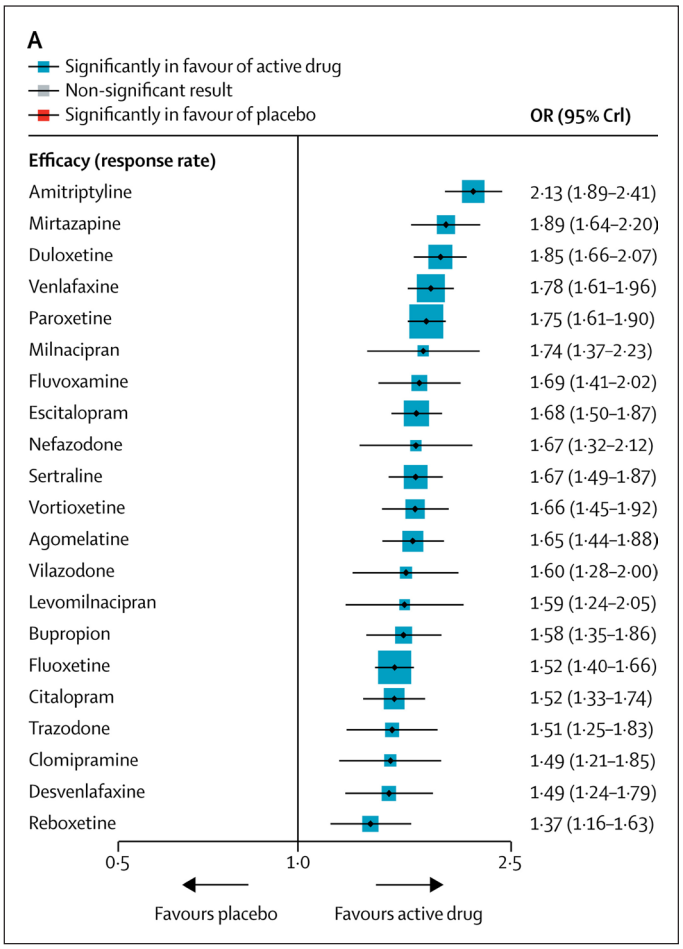
The harmful misconception that antidepressants are 'no better than placebo' is a popular one, making the rounds year after year. Equivocations like this are not only false but a gross misrepresentation of the evidence. A new meta-analysis published in the Lancet will hopefully take this falsehood behind the barn and put it down for good. Antidepressants are incontrovertibly effective when prescribed appropriately to patients suffering from moderate to severe major depressive disorder. This is not always the case however, and herein lies the problem. Patients who are mildly depressed or simply unhappy are inappropriately prescribed, yet these conditions do not meet the prescribing criteria and have no strong evidence of effectivity. Modern antidepressants are not designed for this use: they are not 'happy pills'.

This notion of 'no better than placebo' likely came about from a widely critiqued meta-analysis published in 1998 that claimed 75% of antidepressants' effects were due to placebo and suggested the remaining 25% were likely placebo as well. Further, in 2008 a New England Journal of Medicine review found a strong publication bias in the reporting of antidepressant effects. The published studies showed a rate of positive results of 94%, but this figure fell to 51% after including the unpublished trials as well.

They stated: "Selective reporting deprives researchers of the accurate data they need to estimate effect size realistically. Inflated effect sizes lead to underestimates of the sample size required to achieve statistical significance. Underpowered studies — and selectively reported studies in general — waste resources and the contributions of investigators and study participants, and they hinder the advancement of medical knowledge. By altering the apparent risk–benefit ratio of drugs, selective publication can lead doctors to make inappropriate prescribing decisions that may not be in the best interest of their patients and, thus, the public health."

A later analysis of this study showed that the results were misunderstood or misrepresented. Every single



Results of drug efficacy versus placebo (Cipriani et al, 2018)

drug analyzed was in fact better than placebo, but not to the degree that published literature would suggest. So even though the effect size may be up for debate, drug efficacy is not.

A new 2018 study reviewed data from 522 randomized double-blind controlled experiments which tested 21 antidepressant drugs. They attempted to include as much unpublished data as possible. This dataset consisted of more that 115,000 patients who were properly diagnosed with major depression and treated with antidepressants for at least 8 weeks. The criteria that this study established for effectivity of the drug was a 50% or greater reduction of symptoms based on physician evaluations, which are far more accurate than self-report information. These modern techniques found that every one of the 21 antidepressants tested was significantly more effective than placebo.

The diagram above shows the results from this study. Each of the blue boxes indicate the odds ratio, showing how much more effective the drug was than the placebo. Amitriptyline performed the best, being rated as 2.13 times more likely to reduce symptoms than the placebo. The black lines indicate confidence bars, meaning that the study showed 95% certainty that the results lie within the range of the black line. Importantly, none of the confidence lines cross the '1' mark. This means that even if the estimate is somewhat inaccurate, the drug is still more effective than placebo.

Though every drug analyzed worked above placebo, it is also important to note the wide disparity between various drugs. For example, Fluoxetine (Prozac), was among the least effective, even though it is still widely prescribed. Another interesting aspect of the study is the patient dropout rate. The rate of patients who do not complete a study is a good indication of a drug's side effects. Clomipramine had the highest rate of patient dropout. This information is all publicly available and will help physicians make the best decisions in the future.

This new study is very comprehensive, rigorous, and impressive. The evidentiary support for the efficaciousness of modern antidepressant medication is simply overwhelming. Going forward, this study should arm responsible healthcare providers against denialists' attacks on science. As a scientific discipline, there is ongoing room to improve our knowledge about dosing, effect size, and other prescription guidelines, but the data is conclusive that all these drugs do work significantly better than placebo. Depression is a serious illness that takes the lives of thousands. Antidepressants save lives, relieve suffering, and provide critical quality of care for an embattled patient population. It is vital to defend their efficacy and use when the science so clearly backs them up.

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Use of Gastroprotectant Drugs against Peptic Ulcer Disease

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Peptic ulcer disease (PUD) is a consequence of the breakdown of the lining of the gastrointestinal tract. PUD is classified by ulcers in the stomach, duodenum or the esophagus. Some symptoms of PUD include bleeding, anemia, dysphagia (difficulty swallowing), and recurrent vomiting.

PUD can be a result from a bacterial H. pylori infection or NSAID painkiller overuse. The bacteria, *H. pylori*, embeds itself into the protective mucosa of the stomach and duodenum, weakening it. *H. pylori* is able to survive acidic conditions because of the alkaline enzymes it secretes that neutralizes the acids and allows it to continue burrowing within the lining. NSAIDs, like aspirin, function by suppressing prostaglandin synthesis, resulting in decreased gastric mucosal blood flow which can eventually lead to damage of the mucosa. Additionally, a suppression of prostaglandin synthesis can result in increased gastric acid synthesis and decreased bicarbonate synthesis, further weakening the gastric lining defense. So in short, uncomplicated PUD can be merely treated by eliminating the *H. pylori* infection or decreasing the use of NSAIDs.

However, some cases of PUD are more complicated and require gastroprotectant drugs which can heal the mucosa, stabilize bleeding of the gastrointestinal tract, and additionally protect the mucosa from further damage. Gastroprotectant drugs can be in the form of proton–pump inhibitors (PPIs), prostaglandin analogues, and histamine-2 receptor antagonists (H2RAs). PPIs are responsible for inhibiting the H^+/K^+-ATPase on parietal cells of the stomach, decreasing acid secretion. Prostaglandin analogues function similarly to prostaglandins and inhibit gastric acid secretion and additionally stimulate bicarbonate secretion.

In a study discussed by an article in *The Lancet*, PUD patients were assigned to either a prevention trial, healing trial or treatment of acute upper GI bleeding trial. Each trial group was randomly given either a PPI, prostaglandin analogue, or H2RA.

In the prevention trials, gastroprotectant drugs reduced the development of endoscopic ulcers and

upper gastrointestinal bleeding. In contrast to the other drugs, PPIs showed a more significant reduction in upper gastrointestinal bleeding. It was also found that PPIs were more effective than prostaglandin analogues and H2RAs when it comes to ulcer healing and protectiveness from further bleeding. Gastroprotectants, PPIs in particular, reduce the risk of peptic ulcer disease and its complications and promote healing of peptic ulcers in a wide range of clinical circumstances.

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JAMA Study: 5-Year Weight Loss After Roux-en-Y Gastric Bypass Procedure

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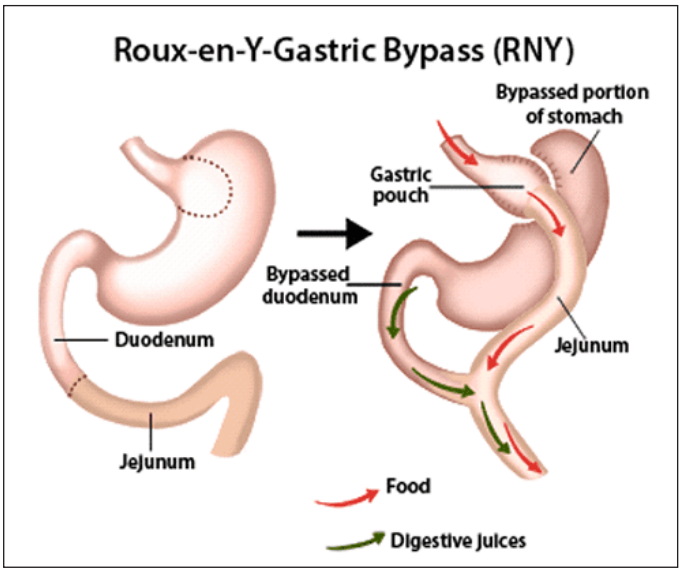
An insightful new study published in the *Journal of the American Medical Association (JAMA)* presents evidence that two well-known surgical procedures intended to help obese patients lose weight produce nearly identical results in terms of changes to body mass index (BMI) 5 years following the procedures.



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The research, conducted by the Swiss Multicenter Bypass or Sleeve Study, followed 217 morbidly obese patients who were evaluated for bariatric surgery from January 2007 to November 2011. From this group, 107 patients were advised to undergo laparoscopic sleeve gastrectomy and 110 received laparoscopic Roux-en-Y gastric bypass. Sleeve gastrectomy, considered a faster, less technically complex surgery, involves removing approximately 85% of the stomach by excising a large portion of the organ along its greater curvature. In contrast, Roux-en-Y is a more time-intensive and complex operation in which the stomach is reduced to a very small pouch that is directly attached to the jejunum of the small intestine. Then the intestinal section of the stomach and duodenum that is severed is sewn shut at the stomach's esophageal end and also attached to the jejunum at the duodenal end creating the "Y" junction that it is characterized by. In this manner, ingested food passes through a much smaller stomach pouch, however the larger, separated stomach remnant is still able to provide important gastric enzymes to aid in the process of digestion.

Five years post procedure, the patients who underwent sleeve gastrectomy reported a reduction in their excess BMI of 61.1% and patients who underwent Roux-en-Y reported a reduction of 68.3%, indicating that both operations achieved almost the exact result in terms of weight loss. This can be interpreted as significant, since despite the fact that sleeve gastrectomies are being carried out with increasing frequency, there is currently little evidence that shows that they are effective in the long term.

One notable exception to the general conclusion that results obtained from both procedures were relatively similar is that patients who underwent sleeve gastrectomy were more likely to continue to suffer from Gastrointestinal Reflux Disease (GERD) or even experience worsening of the disease symptoms. In examining how the two procedures are carried out, one might have hypothesized that this could be a possible finding given that in a sleeve gastrectomy, the general structure of the stomach and midgut remains intact, which could allow existing reflux issues to remain. In comparison, in a Roux-en-Y procedure, the stomach is reduced to an egg-sized pouch and the vast majority of the gastric-enzyme producing stomach is disconnected from the esophagus thus theoretically lessening the potential of gastric juices to reflux into the esophagus.

Another important finding in this study was that neither procedure could be shown to provide an advantage in remission rates of type II diabetes. The Swiss team cited other studies showing that Roux-en-Y typically provides a superior rate of diabetes

remission in patients in the long term when compared to sleeve gastrectomy. However, no evidence could be found in the current study to support this conclusion.

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Dabigatran in Antithrombotic Therapy

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Patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) require treatment with anticoagulation to reduce the risk of thromboembolic events and death. Previous guidelines recommended that these patients receive triple therapy with warfarin, a P2Y12 inhibitor such as clopidogrel or ticagrelor, and aspirin. However, this approach is associated with a significant risk of bleeding. The authors of the study sought to compare the efficacy of dual antithrombotic therapy with dabigatran, an oral, direct thrombin inhibitor, and a P2Y12 inhibitor versus triple therapy that included warfarin. Patients were treated for an average of about 12 months, and the results of the trial indicated that dual therapy that included dabigatran had a significantly lower risk of bleeding compared to triple therapy with warfarin. Additionally, dual therapy with dabigatran was non-inferior to triple therapy with warfarin with respect to prevention of stroke, thromboembolic events, or death. The relative risk of bleeding and thromboembolic events must be carefully weighed on an individual basis. Physicians must take all patient risk factors into account before initiating anticoagulation. Nonetheless, the results of this study indicate that clinicians can be comfortable treating patients with atrial fibrillation who have undergone PCI with dual therapy that includes dabigatran, as these patients will achieve a relatively safe and therapeutic degree of anticoagulation.

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The Perfect Match: Fighting Pediatric Illness with Art and Education

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Photo by Lior Fusman

When a child is admitted to a hospital, they are often overcome with fear and anxiety. It is particularly difficult for pediatric patients to tolerate the medical experience of painful procedures and intimidating interactions with hospital staff without feeling overwhelmed. Additionally, the sick child often requires additional assistance beyond standard hospital accommodations, such as caring visitors, recreation, education, and near-constant companionship. Furthermore, hospitalizations interrupt children's routines, thus threatening their senses of stability and security. The negative but unavoidable repercussions to hospital admissions for pediatric patients can be detrimental to their physical healing and overall medical experience.

A central goal in pediatric health care is to facilitate the emotional and physical wellbeing of the child throughout their stay in order to improve medical healing. In 2008, Dr. Donna Koller, PhD, from the Hospital for Sick Children in Toronto, Canada,

conducted a study assessing the value of play for children in hospitals. She reported the tremendous value of therapeutic play on the overall wellbeing of admitted children, accomplished by reducing the psychological and physiological stresses pervasive in hospital stays. Dr. Koller's findings also indicated that therapeutic play during hospitalizations had long term benefits and was correlated with more positive behavioral responses at future doctor visits and medical experiences.

Therapeutic play is proven to reduce negative physiological responses often associated with stress. Two studies show that children who were provided opportunities for therapeutic play demonstrated less physiological distress, as indicated by lower blood pressure, pulse rate, and less palm sweating; these data indicate that therapeutic play clearly has a significant role in the physiological responses of fear and anxiety in pediatric patients [2, 3]. Dr. Koller concludes that therapeutic play should remain the focus of ongoing critical analysis and further research to help meet the emotional and psychological needs of pediatric patients [1].

Students at Yeshiva University, recognizing the importance and absence of therapeutic play in pediatric hospital care, created the Together Educating all Children in Hospitals (TEACH) project. Through TEACH, college and graduate students curate enriching educational activities and the opportunity to socialize with nonmedical staff for hospitalized children. TEACH's curriculum includes a series of science modules created to support and comfort both hospitalized patients and their siblings. TEACH science modules are recreational activities, designed to provide entertainment and convey engaging scientific concepts. Sample TEACH modules include building model bridges out of gumdrops, creating a circuit to make an LED light glow, assembling roller coasters out of foam tubes, or making lava lamps and bouncy balls. Each module offers a multifaceted learning opportunity that promotes bonding within the family, as well as between the patient and the hospital staff. By creating a space to facilitate therapeutic and educational play with patients, TEACH helps them through their admission in a sustainable and positive way.

TEACH has been implemented at both Dana-Dwek and Schneider Childrens' Hospitals in Israel. Sackler School of Medicine students have the opportunity to volunteer with a TEACH team leader in performing and executing the modules in either of these hospitals. To further understand the benefits of therapeutic play, TEACH in Israel is conducting an ongoing study to determine the effectiveness of educational-based childhood play versus conventional non-educational activities in the hospital setting. The students at Sackler School of Medicine are fortunate to be a part of this new educational and therapeutic approach in the hospital setting. TEACH brings a unique venue of creative and mind-stimulating entertainment for patients to enjoy, and continues to be a success by bringing positive experiences to the pediatric patients of Israel.

Special thanks to Dr. Tali Capua and Miriam Klar

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