Journal of High School Science

The forgotten placebo: A correlational study between tablet angularity and intended use in common American psychotropics

Johansson K

Submitted: August 8, 2023
Accepted: September 16, 2023

Abstract

The placebo effect is well established in the pharmaceutical field for enhancing patient compliance, persistence, and perceptions of drug efficacy. Effective utilization of the placebo effect is often researched through color and overall pill shape. The intentional use of tablet angularity, however, has not yet been evaluated. This study sought to determine a relationship between angularity and intended use in the most common stimulants and depressants prescribed in the U.S. through the analysis of databases provided by the National Institutes of Health, Physicians' Desk Reference, and Drugs.com. In order to investigate the data, a mean square contingency test using the phi coefficient and a verifying chi-squared test of independence were performed. This analysis found that while there was variety in tablet angularity, it did not correlate with the perceived intended benefit of the sample. Further research is needed in the deliberate design of pill shape so as to maximize the placebo effect, and consequently; the efficacy of psychotropic drugs.

Keywords

Placebo, Placebo effect, Drug efficiency, Drug marketing, Psychotropic, Pill shape, Stimulant, Depressant, Phi coefficient, Angularity

---

Kristen Johansson, Hunterdon Central Regional High School, 84 NJ-31, Flemington, NJ 08822, USA. kristenjohansson20@gmail.com

Introduction

Scientific research unlocks many of life's mysteries. Its value through the ages cannot be disputed. Yet, there is much that still needs to be uncovered. Pharmacology is a popular area of research, constantly teeming with academic curiosity and new theories. Unfortunately, mental illness and its treatment have long been overlooked until recent years. Its dark, tragic past can be enlightened with research. Specifically, attention must be brought to psychiatric drugs, as the number of Americans taking these medicines has been continuously increasing, and by 2020, "16.5% of adults had taken prescription medication for their mental health,"(1). Since this number represents a significant portion of the American population, and because it continues to rise, achieving the maximum benefit of these drugs with minimal associated risks is more important than ever. The millions who suffer from mental illness deserve that all facets that prove the efficacy of psychotropic drugs be explored.

Literature review

In order to attain this goal, both medication adherence, as well as perceptions of efficacy, must be addressed. It has been established that the placebo effect– inactive features, ingredients, or beliefs about a pill having an active role in its perception of efficacy– is a particularly strong phenomenon in psychiatric medications (2,3). This effect is pertinent to maximizing both patient compliance as well as perceived efficacy.

Compliance, or persistence, is a critical factor to drug success (4), if a patient continues to take a medication for the required length of time, the active compound has more time to work, and therefore, the drug will have a greater chance of meeting predetermined clinical end points. The relationship between compliance and perceived efficacy was demonstrated in the work of Kesselheim et al. (5) where the team evaluated the effect of a change in shape or color on non-persistence. In the shape portion of this study, a sample of 11,513 patients were evaluated, 3286 (29%) of which had a change in pill shape. In addition, the team conducted a similar portion of the study with a color change. They discovered that after a change in pill shape, 66% of patients discontinued their medications. Similarly, after a change in pill color, 34% of patients discontinued their medications. This data is significant in demonstrating the need for thoughtful pill design in the psychiatric field. In other words, if pharmaceutical companies are meticulously intentional when designing pills, it will be less likely such companies will need to change pill shape in the future. With less shape change, the risk of non-persistence is decreased. This represents the importance of maximizing shape and color placebos in order to increase patient compliance, and therefore drug efficacy.

In addition to long-term increases in drug efficacy due to patient compliance, the placebo effect also offers short-term increases in perceptions of efficacy. This phenomenon was observed in the work of Amawi and Murdoch (6), who concluded that different colors consistently evoked different benefits to patients. For example, red proved to be more stimulating, while blue proved to be more calming. Likewise, the work of Schapira et al. (7) was able to conclude that patients who had pills dyed more "calming" colored felt that their anxiety symptoms improved. Both

Schapira et al. as well as Amawi and Murdoch concured that congruence between a pill's inert factors, in this case color, and intended benefit, in this case calming or stimulating, improved a drug's perceived efficacy. This increase in perceived efficacy is directly linked to a reduction in perceived symptoms. Hence, the placebo effect is extremely relevant to the pharmacology field, to increased drug efficacy, not only through compliance as seen by Kesselheim et al., but also through short-term perceptions as illustrated in the studies of Amawi, Murdoch and Schapira et al. The use of inert factors to maximize active compounds' performance allows for a risk minimization and efficacy maximization strategy, as many drugs present unpleasant side effects when doses are increased unnecessarily (8-10).

Despite the side effects avoided through maximizing the placebo effect, the use of color in the form of Food Drug & Cosmetic (FD&C) dyes in drugs presents a controversy. There is abundant evidence establishing that the proprietary labeled excipients like FD&C dyes and sweeteners are increasing in both prevalence and concentration in U.S. products (11). Not only are these dyes increasingly common, but they are also found in dangerous quantities in places where labeling regulations are more lax. For example, the research of Kulkarni et al. found that Indian pharmaceuticals had mislabeled excipients and concerning levels of additives and dyes (12). That same year, Kumar et al. (13) proved this research to be mirrored in the U.S., since the prevalence of dyes and certain preservatives was also observed to be higher than reported. The work of Lehmkuhler et al. (14) confirms the conclusions of Kulkarni and Kumar in a more modern context. Lehmkuhler also expanded upon the work of these two groups by extending the research into the field of over-the-counter (OTC) products where they studied vitamins, prenatals, and syrups. All of these OTC products exceeded the daily limits set by the FDA. This once again exemplifies the improper labeling seen in the work of Kulkarni. The significance of the mislabeling and poor regulation seen in this study was supported by the findings of researchers like Bateman et al (15), who concluded through meta-analysis that excipients like dyes and preservatives can negatively affect the behavior of children and cause hyperactivity. This study also concluded that limiting these dyes was important for reducing the risk of hyperactive behavior and negative side effects. Due to the controversy regarding the significant risks and dishonest labeling of FD&C dyes (11-19), it is important to consider alternative avenues to these ingredients to maximize a placebo effect while minimizing unnecessary risks.

Despite the risks associated with dyes, Sarpatwari et al. (20) found that 72% of research participants relied on pill color to determine if they took the correct medication. Therefore, there is certainly a function to color, however, the same individuals did not value the pill color enough to pay a $1 premium on a $5 copay to keep the color. Thus, although “requiring uniform pill appearance may help increase adherence,”(20) this is not of paramount importance. On the other hand, research by Kesselheim et al. (21) concluded that pill color was directly linked with adherence to medication and was therefore critical. However, this study was performed only on patients taking one of three MI drugs after hospital dispatch. In addition, Kesselheim et al. (21) found data following the results of

Khan et al. (22) that compliance was more negatively influenced by a change in pill shape than color, (66% vs 34% odds of non-persistence). This suggested that when dyes were removed, pill shape offered a way to identify pills, ultimately reducing the risk of non-persistence. This finding offers a solution to the discrepancy presented by Sarpatwari et al.; patients wish to identify and know they took the correct medication, but do not necessarily value that this identification is through color. Therefore, there is disagreement between researchers on the value of pill color. This conundrum may be solved through thoughtful use of shape.

Although many studies focusing on maximizing the placebo effect focus on color perception in dyed pills, both shape and unique form offer a similar, if not more effective, effect. However, the work of Khan et al. (22) found that "pharmaceutical companies [do not] color and formulate the shape of drugs to enhance the treatment response", but rather shape the drug in capsule form for extended-release options, or tablet form for a faster release. This incongruence is significant in determining that that shape is not an effective way to maximize drug efficacy, because the unique benefits of capsule vs. tablet outweigh the placebo response that may differ from individual to individual.

However, Khan et al. (22) also found that "55% of psychotropics [in the U.S. market] were tablets" in 2010. Therefore, if the placebo effect can be maximized in the unique form of these tablets, *viz.* their angularity, a significant impact can be made on the efficacy of psychotropic drugs.

The work of Blazhenkova et al. (23) demonstrated the placebo effect in terms of tablet angularity by finding that perceptions of more angular pills were more stimulating and that more round pills were more calming. In addition, Blazhenkova et al. theorized in their study that "the choice of the shape of pills and supplements is rather arbitrary, irrelevant to the claimed benefit of the drug". However, this hypothesis was based on the juxtaposition of tablets with angular edges and calming intended benefits in the Turkish market, but not based on an actual evaluation of the overall market. Additionally, this incongruence is yet to be evaluated in the literature, and the correlation between angularity and intended use in the current population of U.S. psychotropics is unknown. In other words, no research to date has evaluated how pharmaceutical companies take advantage of the effect that angularity may have on efficacy.

This research attempted to fill this gap in the literature by evaluating how effective pill angularity is currently being utilized in US psychotropics. To do so, the correlation of angularity with the intended benefit of the most common prescription stimulant and depressant tablets in the U.S was explored.

This research will be the first to evaluate if tablet angularity is currently being used effectively in U.S. psychotropics. Based on the findings of previous studies, namely those of Blazhenkova et al. (23), the hypothesis of this study was that angularity and intended stimulating benefit are negatively correlated. This would mean that psychotropic tablet manufacturers are not currently employing the most recent findings, and therefore are not

maximizing the efficacy of their drugs through angularity.

It is critical to understand both the direction and magnitude of the correlation between angularity and intended use in current psychotropics to determine if more attention must be paid to thoughtful design. Thoughtful design is key, for changes in design can lead to non-persistence in the short term (4-5). Therefore, it is crucial that the areas where congruency between these variables does not occur receive more attention, and on the other hand, the areas that already have a strong degree of correlation do not need to trade persistence for an unnecessary change in pill angularity. Ergo, this study provides context as to whether or not designing and editing psychotropic unique forms is necessary.

Similarly, the unveiling of this relationship between angularity and intended use will offer insight into the market to pharmaceutical companies and marketers who wish to sell more of their drugs. A more congruent relationship between angularity and intended benefit suggests a greater placebo effect of the drug, and thus a drug perceived as being more effective (2-3,5-7,20,22,23). Generally speaking, when a drug is perceived as more effective the consumer will be more likely to continue taking that brand of medication (5,21). This continuance of consumption can be associated with an increased opportunity for producer revenue, which is in the pharmaceutical companies' best interest in terms of desirable profit from increased drug sales.

Materials and methods

A correlational analysis was performed to evaluate if tablet angularity is currently being used effectively in U.S. psychotropics. Data was collected and analyzed for the 15 most commonly prescribed stimulants and depressants.

Methods

Correlational research analyzes variables in their natural environments to define a relationship between them (24). The variables are not manipulated but rather, data is collected after they are set.

This method is cost-efficient and has little demand for additional resources in the context of this study. However, correlational research is limited in what it can deduce, being that correlation does not equate to causation (24). This method, therefore, provides little room for inference as to what factors underlie the correlation. Additionally, the sample must be representative of the population. In the context of this study, this indicates the need for clearly defined variables: angularity and intended benefit.

Despite its limitations and opportunities for bias, correlational research avoids bias presented by other methods when data collection is done objectively (25). For example, because correlational research does not involve data manipulation, it does not foster the same biases experimental methods may encounter.

Correlational research was suitable for this study, as it was pertinent to the research goal of evaluating the current U.S. prescription psychotropic market for efficacy in the utilization of pill angularity as a placebo effect.

To evaluate this, a relationship between pill angularity and intended benefit in the current market was determined. The nature of a correlational study allowed the description of a relationship between angularity and intended use while maintaining their independence from each other. Determining this relationship may help to fill the gap in the literature by uncovering the current state of the US psychotropic market and how pharmaceutical companies are utilizing new research to begin the process of evaluating if there is any thoughtful intention regarding pill angularity.

Data sample

A sample of stimulant (n=47) and depressant (n=29) doses was included in the study. This sample consisted of different active compounds and brand names including 4 stimulant drugs and 9 depressant drugs. Employing a larger sample size representative of the most frequently prescribed psychotropics succored to limit the potential of a skewed and inaccurate correlation, often referred to as an illusory correlation (26).

Although there are other categories of psychotropics, the central nervous system (CNS) stimulants and depressants were deemed to be the only psychotropic categories with naturally (discrete) dichotomous intended benefits. In other words, stimulants and depressants have a clearly defined use, which is naturally divided into two groups rather than lying on a spectrum (27). Other psychotropics include antidepressants, antipsychotics, and mood stabilizers (28); albeit stimulating and calming in thief chemical nature, these drugs do not always offer an explicitly stimulating or calming intended benefit (29), and were therefore excluded from the study. This distinction is important to assessing congruence, as previous research has only established parallels between stimulating and calming intended benefits, while no research has examined the potential effects of the gray area in between.

In order to select the sample, The National Institute on Drug Abuse (NIDA) pages on (CNS) stimulants (30) and CNS depressants (31) was consulted. While a search for the most commonly prescribed stimulants and depressants yielded numerous results, NIDA was selected as the most accurate data source. The data provided by NIDA was optimal for this study because it was credible, objective, and accessible. NIDA is a branch of a reputable government agency, the National Institutes of Health (NIH). In addition, this branch has access to all government-protected data on prescription rates and is therefore most capable of providing an objective sample of the most common drugs in a category. The publications were able to be used without permission, for they explicitly note that they are “available for your use and may be reproduced in its entirety without permission from NIDA,”(30,31).

Data collection

For each of the sampled drugs, the Prescribers Digital Reference (PDR) (32) was consulted to collect data. The PDR is a subdivision of the Physicians' Desk Reference suite of services. While the credibility of PDR is the subject of a debate in the medical field (33-35), the opposition argues that since its data is sourced directly from FDA-approved drug package inserts, “the PDR is thus a negotiated effort of commercial enterprises and governmental regulators,”(33). However, both those opposed to as well as those in favor of PDR’s use in a

clinical setting agree that the PDR provides researchers with objective data on dosing and indications for use (32-35). According to the PDR webpage, it is “the most recognized drug information reference available in the U.S.,”(32). This claim is particularly significant, as the use of the PDR offers objective data on the drugs sampled. The intended benefit, stimulating or calming, of each dose of each drug was able to be determined. Using the PDR for this purpose removed the opportunity for biased data, which would propose a concern for alternate databases (36).

After charting the dosages and form, the intended benefit for each drug sampled was recorded. In this study, all stimulants were found to have a stimulating intended benefit while all depressants were found to promote a calm state (37-40).

In addition to accessing the PDR, data was also collected on the angularity of each drug. As no study to date has attempted to measure angularity in this context, extra consideration was put into the best method of doing so. Finally, Drugs.com (41) was chosen as the data source for this task. Drugs.com acknowledges itself as “the largest, most widely visited, independent medicine information website available on the Internet,”(42). This claim is solidified by a cross-sectional study of 1875 pharmacists, which found that the most commonly used database amongst the sample was drugs.com (43). In addition to its popularity, Drugs.com aims “to be the Internet’s most trusted resource for drug and related health information[...] by presenting independent, objective, comprehensive and up-to-date information in a clear and concise format,”(42). Evidently, the credibility of drugs.com is established and government organizations such as FDA and NIH recommend its use to both consumers and healthcare professionals as “a reliable website” to stay “better informed” about drugs (44,45). Therefore, Drugs.com was found to be the most appropriate database to determine the angularity of the sampled tablets.

In order to collect this data, the Drugs.com Pill Identifier (46) page for each dose in this study was consulted. On this page, an image of the tablet, as well as a physical description, was provided. The image served as a verification, confirming the physical description as being accurate. The description included the shape of the tablet. According to Drugs.com, the shapes of pills in the US market include the following: Round, Capsule-Shaped, Oval, Egg, Barrel, Rectangle, 3 Sided, 4 Sided, 5 Sided, 6 Sided, 7 Sided, 8 Sided, U Shaped, Figure 8, Heart, Kidney, Gear, Character (46). Those in this sample include the following: Round, Capsule-Shaped, Oval, Rectangle, 3 Sided, 4 Sided, 5 Sided, 6 Sided.

Shapes were coded into either angular or curvy. Tablets are generally produced with rounded edges, as sharp edges pose a danger when swallowed (47,48). Therefore, a clear parameter was defined for angularity, without requiring true angles to be present: shapes that contained one or more straight edges were classified as being angular. On the contrary, curvy pills were defined as those which did not contain a straight edge. From these definitions, angular shapes included the following: Rectangle, 3 Sided, 4 Sided, 5 Sided, 6 Sided; while curvy shapes included: Round, Capsule-Shaped, Oval. Both the shape and the

determined angularity of each drug sampled were recorded.

Data filtration

Following data collection, the sample was then refined by excluding all doses of drugs that were not in the tablet form. Although generic versions of drugs are often consumed, these were omitted in order to align with the research question. By using only brand name drugs, only the companies that held trademarks on drug formulas, and therefore those who strived to be maximally efficient and invest in making their product more preferable than generic versions were evaluated. Drugs and/or doses no longer prescribed in the USA, either because of being discontinued or banned, were not considered in this study.

Analysis

Within the field of correlational research, there are numerous methods of analysis with applicability to this study. When describing which method is most effective at answering the research question, it is important to acknowledge the assumptions of various approaches. In order to do so, only those correlational methods that met the parameters of this study were considered.

The research question involved two variables: intended benefit and angularity. By only using drugs with a clearly defined intended benefit, this variable could be described as a discrete dichotomy. Similarly, the subjectivity of angularity presented the need to define this as a discrete dichotomy as well. For example, a scale of angularity is immeasurable and leaves room for significant researcher bias. In order to reduce this bias, defining angularity by the presence of straight lines established angularity as a natural dichotomy. Since both intended benefit, as well as angularity, are discrete dichotomies, the phi coefficient (φ), or mean square contingency, was selected as the appropriate analytical test.

Phi correlation was the most pertinent test to answer the research question, as similar correlational tests were found to not operate under assumptions aligned with the research question of this study. For instance, Cramer's V operates under the same assumptions as phi but includes more than 2 variables (49). Similarly, Tetrachoric correlation also employs two dichotomous variables, but they must be artificial dichotomies (49,50). Ultimately, phi correlation was selected as the most appropriate method because it measured a relationship between two naturally dichotomous variables, therefore, aligning with the research goal (49,50).

In performing the analysis the bivariate data classified into stimulating vs. calming and angular vs. Curvy was used. The data was entered into a 2x2 contingency table, thereby translating the data from qualitative to quantitative (Table 1). Lastly, the mean square contingency was calculated per equation 1.

$$\Phi = (AD-BC)/[(A+B)(C+D)(A+C)(B+D)] \quad (1)$$

In this equation, letters A-D represent the numerical values found in each data box in the contingency table created (51, Table 1). This equation yielded a value between -1 and +1. A

value of 0 indicated no relationship, while negative values indicated a negative correlation and positive values a positive correlation (52).

drugs and their corresponding doses, were omitted from this study for various reasons. The filtered sample consisted of 45 doses of 13 psychotropics.

Results

All data was collected and filtered to include only tablets prescribed in the U.S.. During filtration, twenty-five doses across four stimulant drugs, as well as five depressant

In Tables 1 and 2, the distribution of angularity across drug classes is represented by the exact data (Table 1) as well as frequencies as a percentage of the total sample (Table 2).

Table 1. Distribution of Angularity

	Stimulant	Depressant	total
Angular	10	6	16
Curvy	12	17	29
total	22	23	45

Table 2. Relative Frequencies as Percentages

	Stimulant	Depressant	total
Angular	22.22%	13.33%	35.56%
Curvy	26.67%	37.78%	64.44%
total	48.89%	51.11%	100.0%

Table 1 is the 2x2 contingency table used to calculate the mean square contingency and chi-squared (X^2) value for the data. Table 2 used this same data, but presented the values as percentages of the sample. As depicted in Table 2, nearly half of the sample was stimulants. However, only 35.56% of the sample was classified as angular. Correspondingly, there were more curvy stimulants than there were angular (12 vs 10). Similarly, there were also more curvy depressants than there were angular depressants (17 vs 6). Such conclusions can be visualized in Figure 1. While there are more angular tablets than curvy in both classes, it was clear that the distributions of angularity between stimulants and depressants were not identical, thus differences needed to be evaluated.

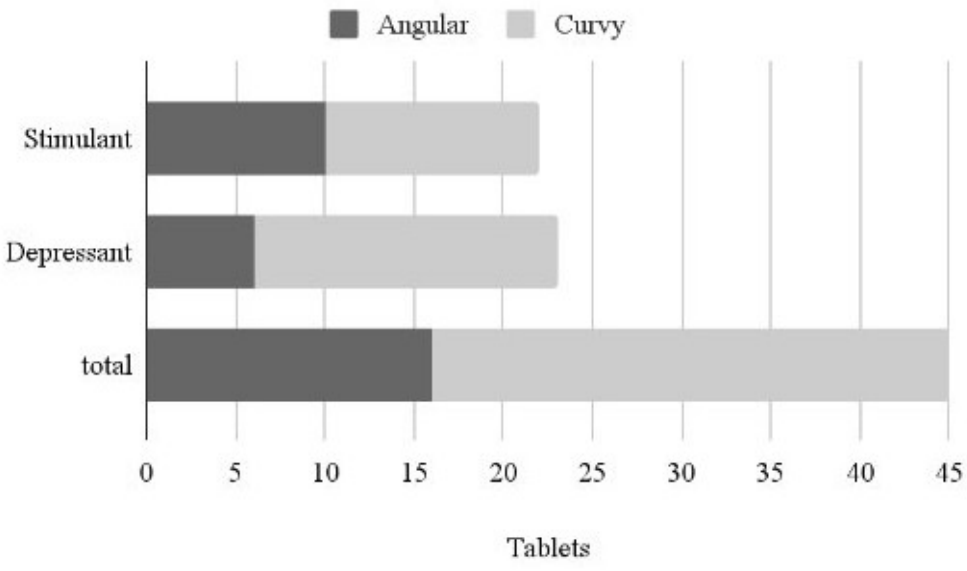

Figure 1. Visualization of the distribution of angularity

Analysis

In order to assess the strength of this relationship as well as its statistical significance, the data from Table 1 was used to calculate the following variables: $r\ \varphi$ = 0.20225, X^2 = 1.84, *p-value* = 0.05, *degree of freedom* = 1, *critical value* = 3.841

The calculated phi coefficient (0.20225) indicates a weak positive relationship between intended benefit and angularity. This suggests that there is a relationship between stimulant pills and angular form as well as depressant pills and curvy form. However, the lack of strength in this relationship further indicates the necessity of a chi-squared test to evaluate its independence.

A p-value of 0.05 was selected, since a 95% confidence interval is the standard for determining statistical significance in the pharmaceutical field (53). The equation $df = (r - 1)(c - 1)$ was used, where r is rows, c is columns, and df is degrees of freedom for a given contingency table to calculate the degree of freedom to be 1. From these values, the critical value for a chi-squared test was calculated to be 3.841. The chi-squared value for this data (1.84) was less than the critical value for 1 degree of freedom and a 95% confidence interval (3.841). Therefore, the weak positive relationship between intended benefit and angularity was not statistically significant and may have been due to chance. Thus, no significant statistical association between intended benefit and angularity was found. This conclusion signified that the aforementioned discrepancies between the distributions of angularity in stimulants and depressants may be due to chance and are, consequently, not statistically significant.

Discussion

The data collected and analyzed using the corresponding statistical tests confirm the null hypothesis by establishing that, while there is variety in angularity, it does not correlate with the intended benefit of the current most

frequently prescribed stimulant and depressant tablets in the U.S. The data also provided credibility to Blazhenkova's prediction that pill and supplement shapes are chosen arbitrarily (23). While similar studies have been performed within the body of pharmaceutics research, for example, that conducted by Khan et al. (22) which found that pharmaceutical companies "do [not] color or formulate the shape of drugs to enhance the treatment response", no prior studies have investigated congruity between angularity and intended benefit. This study attempted to fill this gap.

Despite consistent findings on the placebo effect of various inert factors and their congruence with intended use, it must be noted that the placebo effect observed is dependent upon many factors and will therefore differ from patient to patient (54-57). As a rule, the maximization of a placebo effect will increase a drug's perceived efficacy, however, this may not be true for all patients.

The results of this study are limited and future research is needed to determine whether manufacturers take drug shape into account as a factor to increase drug efficacy. Furthermore, this study was limited to stimulant and depressant tablets; therefore, the results of this study can not be generalized to the entire drug market. Existing literature reports on this trend of incongruence in pill characteristics across more categories than sole angularity or solely psychotropics (2-3,5-7,21-23). This suggests that generalization of these results may be possible in the coming years with further investigation. Such investigation is important, as the field contains numerous stakeholders. For example, this study pertains to consumers, producers, and external stakeholders.

The consumers of stimulants and depressant tablets are those who use such for psychological benefit; often long-term patients, for example, those taking drugs to manage a chronic complaint like Attention Deficit Hyperactivity Disorder (ADHD), but also those looking for acute relief, for instance, those taking a depressant to manage fear on a plane ride. Tablets with angularity congruent to their intended use may provide a greater placebo effect (23), ergo offering an increased perceived efficacy to patients, both long term as well as short term. This perception may also increase patient compliance, which consequently increases the likelihood of drug success in long-term patients (4-5,20-21). Therefore, the finding that this congruence is not intentionally present in all psychotropics is significant to patients, as they may not perceive that they are receiving the most effective medication.

Much research is being performed to reduce the negative consequences of other placebo factors. Take excipient FD&C dyes as an example, which are associated with various symptom presentations, including, but not limited to, ADHD, cancers, and liver toxicity (11-19). While the inclusion of these dyes may increase the placebo effect, thoughtful angularity provides an avenue to do such with minimal adverse effects. Therefore, the finding that producers are not employing thoughtful intention to tablet angularity represents an area in which improvement can be made and research can be focused on to enhance patient response to psychotropics without the risks associated with other added ingredient associated factors.

Similarly, this research affects the manufacturers of psychotropics. The new understanding that tablet angularity within this field is not being used efficiently may be used to promote product differentiation and competition with substitutes. By determining that manufacturers may not be using thoughtful design to maximize the placebo effect, motivation to change design may be offered to competitors producing the same product. This is because product differentiation, "an attempt to shift or to change the slope of the demand curve for the market offering of an individual supplier" (58), offers the manufacturer an opportunity to shift the market away from perfect substitutes and toward a more competitive market. With an increased demand for a specific product, the manufacturer has the opportunity to increase their profit (59), thus congruence in angularity and intended benefit is in the seller's favor, and this research presents an opportunity for manufacturers.

Additionally, it is important to further investigate other classes of drugs besides stimulants and depressants. The question must be posed: is the incongruence found in this study seen across other classes? If so, the need for manufacturer education on efficient placebo use may be needed. Regardless, additional research is also indicated to determine if drugs with more congruent inert factors command a larger market share and are perceived to be more efficacious.

Conclusion

Mental illness is often described as an island of knowledge in a sea of ignorance. Continued research can offer a way to expand this island. This study confirmed the null hypothesis that while there is variety in angularity in stimulant and depressant tablets, it does not correlate with the intended benefit of those tablets which are currently most frequently prescribed in the U.S. There appears to be opportunity to exploit tablet shape in general, and tablet angularity in particular, so that the perceived efficacy of the medication (the placebo effect) is maximized.

References

1. Terlizzi EP, Norris T. Mental health treatment among adults: United States, 2020. NCHS Data Brief, no 419. Hyattsville, MD: National Center for Health Statistics. 2021. https://dx.doi.org/10.15620/cdc:110593

2. Petrie KJ, Rief W. Psychobiological mechanisms of placebo and nocebo effects: Pathways to improve treatments and reduce side effects. *Annu Rev Psychol*. 2019;70(1):599-625. http://doi.org/10.1146/annurev-psych-010418-102907

3. Kirsch I. Placebo effect in the treatment of depression and anxiety. *Front Psychiatry.* 2019;10:407. http://doi.org/10.3389/fpsyt.2019.00407

4. Aronson JK, Hardman M. ABC of monitoring drug therapy. Patient compliance. *BMJ*. 1992;305(6860):1009-1011. http://doi.org/10.1136/bmj.305.6860.1009

5. Kesselheim AS, Bykov K, Avorn J, Tong A, Doherty M, Choudhry NK. Burden of changes in pill appearance for patients receiving generic cardiovascular medications after myocardial infarction: cohort and nested case-control studies. *Ann Intern Med.* 2014;161(2):96-103. http://doi.org/10.7326/M13-2381

6. Amawi RM, Murdoch MJ. Understanding color associations and their effects on expectations of drugs' efficacies. *Pharmacy (Basel)*. 2022;10(4):82. http://doi.org/10.3390/pharmacy10040082

7. Schapira K, McClelland HA, Griffiths NR, Newell DJ. Study on the effects of tablet colour in the treatment of anxiety states. *BMJ*. 1970;2(5707):446-449. http://doi.org/10.1136/bmj.2.5707.446

8. Zhang P, Wang F, Hu J, Sorrentino R. Exploring the relationship between drug side-effects and therapeutic indications. *AMIA Annu Symp Proc*. 2013;2013:1568-1577.

9. Kane JM. Antipsychotic drug side effects: their relationship to dose. *J Clin Psychiatry*. 1985;46(5 Pt 2):16-21. https://psycnet.apa.org/fulltext/1986-12559-001.pdf

10. Daughton CG, Ruhoy IS. Lower-dose prescribing: minimizing "side effects" of pharmaceuticals on society and the environment. *Sci Total Environ*. 2013;443:324-337. http://doi.org/10.1016/j.scitotenv.2012.10.092

11. Stevens LJ, Burgess JR, Stochelski MA, Kuczek T. Amounts of artificial food dyes and added sugars in foods and sweets commonly consumed by children. *Clin Pediatr (Phila)*. 2015;54(4):309-321. http://doi.org/10.1177/0009922814530803

12. Kulkarni ML, Sureshkumar C, Venkataramana V. Colourings, flavourings, and sugars in children's medicines in India. *BMJ*. 1993;307(6907):773. http://doi.org/10.1136/bmj.307.6907.773

13. Kumar A, Rawlings RD, Beaman DC. The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations. *Pediatrics*. 1993;91(5):927-933. http://doi.org/10.1542/peds.91.5.927

14. Lehmkuhler AL, Miller MD, Bradman A, Castroina R, Mitchell AE. Certified food dyes in over the counter medicines and supplements marketed for children and pregnant women. *Food Chem Toxicol*. 2020;143(111499):111499. http://doi.org/10.1016/j.fct.2020.111499

15. Rowe KS, Rowe KJ. Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study. *J Pediatr.* 1994;125(5 Pt 1):691-698. http://doi.org/10.1016/s0022-3476(94)70059-1

16. Potera C. The artificial food dye blues. *Environ Health Perspect*. 2010;118(10):A428. http://doi.org/10.1289/ehp.118-a428

17. Food Dyes: A Rainbow of Risks. Center for Science in the Public Interest. https://www.cspinet.org/resource/food-dyes-rainbow-risks

18. Al Humaid J. Sweetener content and cariogenic potential of pediatric oral medications: A literature. *Int J Health Sci (Qassim)*. 2018;12(3):75-82.

19. Arnold LE, Lofthouse N, Hurt E. Artificial food colors and attention-deficit/hyperactivity symptoms: conclusions to dye for. *Neurotherapeutics*. 2012;9(3):599-609. http://doi/org/10.1007/s13311-012-0133-x

20. Sarpatwari A, Gagne JJ, Lu Z, et al. A Survey of Patients' Perceptions of Pill Appearance and Responses to Changes in Appearance for Four Chronic Disease Medications. *J Gen Intern Med.* 2019;34(3):420-428. http://doi.org/10.1007/s11606-018-4791-1

21. Kesselheim, A. S., Misono, A. S., Shrank, W. H., Greene, J. A., Doherty, M., Avorn, J., & Choudhry, N. K. (2013). Variations in pill appearance of antiepileptic drugs and the risk of nonadherence. *JAMA internal medicine,* 173(3), 202–208. http://doi.org/10.1001/2013.jamainternmed.997

22. Khan A, Bomminayuni EP, Bhat A, Faucett J, Brown WA. Are the colors and shapes of current psychotropics designed to maximize the placebo response? *Psychopharmacology (Berl)*. 2010;211(1):113-122. http://doi.org/10.1007/s00213-010-1874-z

23. Blazhenkova O, Dogerlioglu-Demir K. The shape of the pill: Perceived effects, evoked bodily sensations and emotions. *PLoS One.* 2020;15(9):e0238378. http://doi.org/10.1371/journal.pone.0238378

24. Lau F. Chapter 12 Methods for Correlational Studies. In Handbook of eHealth Evaluation: An Evidence-based Approach. University of Victoria; 2017.

25. Kock F, Berbekova A, Assaf AG. Understanding and managing the threat of common method bias: Detection, prevention and control. *Tour Manag*. 2021;86(104330):104330. http://doi.org/10.1016/j.tourman.2021.104330

26. Fiedler K. Illusory correlations: A simple associative algorithm provides a convergent account of seemingly divergent paradigms. *Rev Gen Psychol*. 2000;4(1):25-58. http://doi.org/10.1037/1089-2680.4.1.25

27. Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med.* 2018;18(3):91-93. doi:10.1016/j.tjem.2018.08.001 https://www.researchgate.net/publication/326885374_User%27s_guide_to_correlation_coefficients

28. Caraci F, Enna SJ, Zohar J, et al. A new nomenclature for classifying psychotropic drugs. *Br J Clin Pharmacol.* 2017;83(8):1614-1616. http://doi.org/10.1111/bcp.13302

29. Mark TL. For what diagnoses are psychotropic medications being prescribed?: a nationally representative survey of physicians: A nationally representative survey of physicians. *CNS Drugs*. 2010;24(4):319-326. http://doi.org/10.2165/11533120-000000000-00000

30. Prescription Stimulants DrugFacts. National Institute on Drug Abuse. Published June 6, 2018. https://nida.nih.gov/publications/drugfacts/prescription-stimulants

31. Prescription CNS Depressants DrugFacts. National Institute on Drug Abuse. Published March 6, 2018. https://nida.nih.gov/publications/drugfacts/prescription-cns-depressants

32. Prescriber's Digital Reference. Physician's Desk Reference®. https://www.pdr.net/

33. Cohen JS, Insel PA. The Physicians' Desk Reference. Problems and possible improvements. *Arch Intern Med*. 1996;156(13):1375-1380. https://doi.org/10.1001/archinte.1996.00440120021003

34. Jones JV. The PDR: another view. Arch Intern Med. 1997;157(5):576. http://doi.org/10.1001/archinte.1997.00440260144021

35. Burkhart CG, Burkhart KM, Burkhart AK. The Physicians' Desk Reference should not be held as a legal standard of medical care. *Arch Pediatr Adolesc Med.* 1998;152(6):609-610.

36. Kheshti R, Aalipour M, Namazi S. A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. *J Res Pharm Pract.* 2016;5(4):257-263. http://doi.org/10.4103/2279-042X.192461

37. Drug fact sheet: stimulants. . Department of Justice/Drug Enforcement Administration. Dea.gov. https://www.dea.gov/sites/default/files/2020-06/Stimulants-2020.pdf

38. Drug fact sheet: amphetamines. Department of Justice/Drug Enforcement Administration. Dea.gov. https://www.dea.gov/sites/default/files/2023-02/Amphetamines%202022%20Drug%20Fact%20Sheet_0.pdf

39. Drug fact sheet: depressants. Department of Justice/Drug Enforcement Administration. Dea.gov. https://www.dea.gov/sites/default/files/2020-06/Depressants-2020.pdf

40. Drug fact sheet: benzodiazepines. Department of Justice/Drug Enforcement Administration. Dea.gov. https://www.dea.gov/sites/default/files/2020-06/Benzodiazepenes-2020_1.pdf

41. Prescription Drug Information. Drugs.com. https://www.drugs.com/

42. About. Drugs.com. https://www.drugs.com/support/about.html

43. Qadus S, Naser AY, Al-Rousan R, Daghash A. Utilization of drug information resources among community pharmacists in Jordan: A cross-sectional study. *Saudi Pharm J.* 2022;30(1):1-7. http://doi.org/10.1016/j.jsps.2021.12.001

44. Center for Drug Evaluation, Research. How can I stay better informed about drugs? Is there a reliable website FDA recommends? U.S. Food and Drug Administration. Published November 3, 2018. https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/how-can-i-stay-better-informed-about-drugs-there-reliable-website-fda-recommends

45. How do I identify a pill?. Nih.gov. https://support.nlm.nih.gov/knowledgebase/article/KA-04527/en-us

46. Pill Identification Wizard. Drugs.com. https://www.drugs.com/imprints.php

47. Schiele JT, Schneider H, Quinzler R, Reich G, Haefeli WE. Two techniques to make swallowing pills easier. *Ann Fam Med.* 2014;12(6):550-552. http://doi.org/10.1370/afm.1693

48. Radhakrishnan C, Sefidani Forough A, Cichero JAY, et al. A difficult pill to swallow: an investigation of the factors associated with medication swallowing difficulties. *Patient Prefer Adherence.* 2021;15:29-40. Published 2021 Jan 11. http://doi.org/10.2147/PPA.S277238

49. Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med.* 2018;18(3):91-93. http://doi.org/10.1016/j.tjem.2018.08.001

50. Ekström J. The phi-coefficient, the tetrachoric correlation coefficient, and the Pearson-Yule debate. Escholarship.org. Published October 25, 2011. https://escholarship.org/content/qt7qp4604r/qt7qp4604r.pdf?t=lrh0h2

51. Chen, I. Y.-C. (n.d.). *Lecture 4: Contingency Table.* Washington.Edu. https://faculty.washington.edu/yenchic/18W_425/Lec4_contingency.pdf

52. Chedzoy OB. Phi-Coefficient. Encyclopedia of Statistical Sciences. John Wiley & Sons, Inc.. 2006

53. Kennedy-Shaffer L. When the Alpha is the Omega: P-Values, "Substantial Evidence," and the 0.05 Standard at FDA. *Food Drug Law J.* 2017;72(4):595-635.

54. Hafliðadóttir SH, Juhl CB, Nielsen SM, et al. Placebo response and effect in randomized clinical trials: meta-research with focus on contextual effects. *Trials*. 2021;22(1):493. http://doi.org/10.1186/s13063-021-05454-8

55. Kang H, Miksche MS, Ellingsen DM. Association between personality traits and placebo effects: a preregistered systematic review and meta-analysis. *Pain*. 2023;164(3):494-508. http://doi.org/10.1097/j.pain.0000000000002753

56. Jones BDM, Razza LB, Weissman CR, et al. Magnitude of the placebo response across treatment modalities used for treatment-resistant depression in adults: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(9):e2125531. http://doi.org/10.1001/jamanetworkopen.2021.25531

57. Maslej MM, Furukawa TA, Cipriani A, et al. Individual differences in response to antidepressants: a meta-analysis of placebo-controlled randomized clinical trials. *JAMA Psychiatry.* 2021;78(5):490–497. http://doi.org/10.1001/jamapsychiatry.2020.4564

58. Smith WR. Product differentiation and market segmentation as alternative marketing strategies. *J Mark.* 1956;21(1):3. http://doi.org/10.2307/1247695

59. Rattinger GB, Jain R, Ju J, Mullins CD. Principles of economics crucial to pharmacy students' understanding of the prescription drug market. *Am J Pharm Educ.* 2008;72(3):61. http://doi.org/10.5688/aj720361