

The Social Side Effects of Acetaminophen

DISSERTATION

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Dominik Mischkowski

Graduate Program in Psychology

The Ohio State University

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Dissertation Committee:

Professor Jennifer Crocker, Advisor

Professor Baldwin M. Way

Professor Brad J. Bushman

Professor Leah M. Pyter

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Abstract

About 23% of all adults in the US take acetaminophen during an average week (Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002) because acetaminophen is an effective physical painkiller and easily accessible over the counter. The physiological side effects of acetaminophen are well documented and generally mild when acetaminophen is consumed in the appropriate dosage. In contrast, the psychological and social side effects of acetaminophen are largely unknown. Recent functional neuroimaging research suggests that the experience of physical pain is fundamentally related to the experience of empathy for the pain of other people, indicating that pharmacologically reducing responsiveness to physical pain also reduces cognitive, affective, and behavioral responsiveness to the pain of others. I tested this hypothesis across three double-blind between-subjects drug intervention studies. Two experiments showed that acetaminophen had moderate effects on empathic affect, specifically personal distress and empathic concern, and a small effect on empathic cognition, specifically perceived pain, when facing physical and social pain of others. The same two experiments and a third experiment also showed that acetaminophen can increase the willingness to inflict pain on other people, i.e., actual aggressive behavior. This effect was especially pronounced among people low in dispositional empathic concern. Together, these findings suggest that the physical pain system is more involved in the

regulation of social cognition, affect, and behavior than previously assumed and that the experience of physical pain and responsiveness to the pain of others share a common neurochemical basis. Furthermore, these findings suggest that acetaminophen has unappreciated but serious social side effects, and that these side effects may depend on psychological characteristics of the drug consumer. This idea is consistent with recent theory and research on the context-dependency of neurochemical processes. Finally, public health and legal implications of the social side effects of acetaminophen are discussed.

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Dedicated to Kim.

Vita

March 2001	Gymnasium Leopoldinum, Passau
2008	M.S. Psychology, Universität Konstanz, Germany
2008 to 2010	Graduate student, Department of Psychology, University of Michigan
2012	M.A. Psychology, The Ohio State University
2010 to present	Graduate student, Department of Psychology, The Ohio State University

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Chapter 1: The Social Side effects of Acetaminophen

Acetaminophen (or paracetamol, under its international denotation) is the most popular analgesic in the US. Acetaminophen is an effective painkiller and easily accessible over-the-counter (Bertolini et al., 2006; Graham, Davies, Day, Mohamudally, & Scott, 2013; Toussaint et al., 2010). In addition to being the active ingredient in Tylenol®, acetaminophen is present in many other preparations ranging from cold medicines to opioid analgesics. As a consequence, an estimated 23% of all adults in the US consume a drug containing acetaminophen during an average week (Kaufman et al., 2002).

Though its exact mechanism of action is unknown, acetaminophen exerts its analgesic effect in the brain (Graham et al., 2013; Smith, 2009) and, as a consequence, has a variety of effects beyond ameliorating pain. The physical side effects of acetaminophen are well established and generally mild, but can include hepatotoxicity when acetaminophen is consumed above the recommended dosage (Bertolini et al., 2006; Graham et al., 2013; Toussaint et al., 2010). Furthermore, recent research suggests that acetaminophen can have affective and cognitive side effects. Specifically, acetaminophen decreases general hurt feelings (DeWall et al., 2010), reduces defensiveness to existential threat (Randles, Heine, & Santos, 2013), and blunts the sensitivity to positive and negative stimuli (Durso, Luttrell, & Way, 2015). Beyond these findings, the

psychological and social effects of acetaminophen are largely unknown. Given the widespread consumption of acetaminophen (Kaufman et al., 2002), more research on the social side effects of acetaminophen is needed.

Among other factors, effective social functioning in the modern world requires empathic and amicable, non-aggressive interactions (Batson, 1998; Bushman & Huesmann, 2010; Eisenberg & Miller, 1987). Empathy is vital for social functioning because it motivates prosocial behavior and inhibits aggressive behavior (Batson, 1998; Eisenberg & Miller, 1987; Miller & Eisenberg, 1988; Vachon, Lynam, & Johnson, 2014). Aggressive behavior, in turn, is costly for perpetrators, victims, and society as a whole. The productivity and health costs of aggressive behavior has been estimated to be over \$70 billion in the US alone (Corso, Mercy, Simon, Finkelstein, & Miller, 2007). Any factor that decreases empathy or increase aggressive behavior on a large scale is thus of significant clinical and societal importance.

Acetaminophen and Reduced Empathy

Theory and research over the last decade have suggested that empathy for others' pain is fundamentally related to the experience of one's own pain (e.g., Botvinick et al., 2005; Decety & Jackson, 2004; Jackson, Meltzoff, & Decety, 2005; Preston & De Waal, 2002; Singer et al., 2004). Accordingly, empathy for others' pain relies on affect similar to the experience of physical pain (Singer et al., 2004). Observing others in pain (e.g., watching a person receiving a hot probe placed on the hand), activates two paralimbic brain regions that are also activated during one's own experience of pain – the anterior cingulate and the anterior insula (see Lamm, Decety, & Singer, 2011, for a meta-

analysis). This overlap in neural activation has led to the notion that pain and empathy for pain share a common process (e.g., Decety & Jackson, 2004; Preston & De Waal, 2002; Singer, 2009). Psychologically, these findings suggest that the ability to empathize with other people's pain relies on the same psychological processes involved in generating one's own reaction to pain.

Although multiple neuroimaging studies have documented overlap in regions of brain activation during both the experience of one's own pain and empathy for another's pain (Lamm et al., 2011), the psychological implications of this overlap have been less studied (Zaki & Ochsner, 2012). Because pain and empathy for others' pain are fundamentally related, I hypothesized that pharmacologically inhibiting the experience of one's own pain should also inhibit experiences of another's pain. In other words, an analgesic should blunt not only one's own pain but empathy for another's pain as well.

Critically for my hypothesis, acetaminophen reduces neural activity in the anterior cingulate and insula during social rejection, which causes social pain (i.e., hurt feelings) (DeWall et al., 2010). As these same brain areas are also involved in empathy for pain and the experience of pain (Lamm et al., 2011), I hypothesized that the physical painkiller acetaminophen also impairs empathy when witnessing another person in both physical and social pain. I tested this hypothesis in two experiments.

To establish the robustness of the effect, I explored whether acetaminophen could lead to temporary (i.e., state) reductions in different aspects of empathy. Researchers often distinguish between cognitive and affective components of state empathy (Davis, 1994; Decety & Jackson, 2004; Dvash & Shamay-Tsoory, 2014; Preston & De Waal,

2002; Zaki & Ochsner, 2012). Cognitive empathy involves understanding another person's internal state of pain, whereas affective empathy involves experiencing personal distress in response to another's pain and empathic concern for the well-being of the other person in pain. This distinction is thought to reflect basic brain architecture: Cognitive and affective aspects of empathy involve distinct, but related neuronal networks (Fan, Duncan, de Greck, & Northoff, 2011). To explore the psychosocial effects of acetaminophen, I thus explored the effect of acetaminophen on both empathic affect and cognition.

Acetaminophen and Increased Aggressive Behavior

The genetic, neurochemical, and psychosocial factors contributing to aggressive behavior have received considerable attention over the last decades (Bushman & Huesmann, 2010). Among contributing neurochemical factors, the least amount of attention has been devoted to how psychotropic pharmacological agents, such as acetaminophen, influence aggression. Acetaminophen reducing empathy suggests the intriguing possibility that acetaminophen may not only decrease cognitive and affective responsiveness to other people's pain but may also increase the willingness to inflict pain on other people, i.e., aggressive behavior. I tested this hypothesis using data from the same previous two experiments as well as using data from a separate, third experiment.

To identify protective factors inhibiting the effect of acetaminophen on increased aggressive behavior, I explored the moderating role of dispositional empathy. I hypothesized that dispositional empathy may attenuate the effect of acetaminophen on aggressive behavior, because people high on dispositional empathy show less aggression

(Jolliffe & Farrington, 2004; Miller & Eisenberg, 1988; Vachon et al., 2014). As with state empathy, researchers have conceptualized dispositional empathy as a multidimensional construct, distinguishing between cognitive and affective components (Davis, 1983; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004; Mehrabian & Epstein, 1972). I measured cognitive and affective dispositional empathy using the affective and cognitive subscales of the Interpersonal Reactivity Index (IRI; Davis, 1983), and tested whether these aspects of empathy moderated the effect of acetaminophen on aggressive behavior.

Finally, I explored whether the effect of acetaminophen on aggressive behavior can be exacerbated when people get provoked. Interpersonal provocation is a key instigator of aggressive intentions and aggressive behavior (Anderson & Bushman, 2002; Berkowitz, 1990; Bushman & Huesmann, 2010). If acetaminophen increases aggressive behavior, it may do so especially under circumstances that facilitate aggression. Alternatively, acetaminophen may increase aggressive behavior even when people are not provoked because acetaminophen may make people simply less responsive to the pain of other people. I tested these competing hypotheses, re-analyzing all three experiments.

Thesis Overview

In the first experiment, I tested the effect of acetaminophen on indicators of cognitive and affective empathy, specifically reduced perceived pain and personal distress when witnessing another person in physical or social pain (see Chapter 2). I replicated and extended this effect in a second experiment (see Chapter 3), testing the

effect of acetaminophen on empathic affect and cognition in an actual event of social pain as well as in response to pain scenarios. I also tested the effect of acetaminophen on empathic concern for the pain of others because empathic concern is a key driver of prosocial functioning (Batson, 1998). Next, I tested the effect of acetaminophen on increased aggressive behavior in a second set of experiments. I established the effect of acetaminophen on aggressive behavior in a third experiment (see Chapter 4) and extended this finding using data from the first experiment (see Chapter 5). Specifically, I explored whether dispositional empathy attenuated the effect of acetaminophen on aggressive behavior. Using data from the second experiment, I replicated the moderating role of dispositional empathic concern in the acetaminophen/aggression link (see Chapter 6). I also explored whether effect of acetaminophen on increased aggressive behavior was dependent of interpersonal provocation, re-analyzing all three experiments (see Chapter 6). The last part of my thesis discusses the broader theoretical and practical implications of my findings (see Chapter 7).

Chapter 2: Establishing the Effect of Acetaminophen on Reduced Empathy

A first experiment established the effect of acetaminophen on empathy for both physical and social pain. Participants received either acetaminophen or a placebo and 60 min later rated various hypothetical vignettes describing people in physical pain (e.g., cutting a finger) or social pain (e.g., father passing away). I explored the effect of acetaminophen on both empathic affect (i.e., personal distress) and empathic cognition (i.e., perceived pain) when reading about other people's pain. To rule out the possibility that unspecific general affect explained the effect of acetaminophen on decreased empathy, I tested whether acetaminophen flattened general positive and negative affect.

Methods

Participants

Eighty undergraduate students (26 females; $M_{\text{age}} = 19.4$, $SD = 1.44$; 59 Whites, 7 Asian-Americans, 3 African-Americans, 11 mixed race/others) participated for partial course credit toward their introductory psychology requirement. Four participants failed to finish the study, dropping out at various stages during the study. Nevertheless, I retained the data of these participants in my analyses unless they had failed to provide responses on a dependent measure of interest in a specific set of analyses. In this case, I dropped participants from these analyses. I determined sample size based on previous research which indicated a sample size between 30-50 participants per cell was sufficient

to provide sufficient power to detect a behavioral effect of acetaminophen (Durso et al., 2015).

Pharmacological Procedures

After signing up for the experiment, participants received an email informing them about the risk factors associated with acetaminophen (see *Appendix A*) and asked them to refrain from participation if they met any of these risk factors. To facilitate drug absorption, I also asked participants to refrain from consuming food for three hours before the experiment.

Upon arrival, participants were randomly assigned to consume a liquid containing 1000mg acetaminophen ($n = 40$) or a placebo ($n = 40$). This dosage constitutes the recommended extra-strength dose of acetaminophen for adults (McNeil-PPC; <http://www.tylenol.com/safety-dosing/usage/dosage-for-adults>). Acetaminophen and placebo solutions were prepared by Pharmacy Specialists Compounding Pharmacy (Altamonte Springs, Florida; <http://www.makerx.com/>). The experimenter then led participants to individual cubicles. I waited 60 minutes for the drug to take effect before administering measures of general affect and empathy. After completing these measures, participants guessed whether they had received acetaminophen or the placebo. Before participants left, the experimenter reminded them to refrain from taking acetaminophen or drinking more than two alcoholic beverages in the upcoming 15 hours.

Measures

General affect. General affect was measured with the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). Participants rated their

current affect (i.e., *right now*) on 10 positive (e.g., *excited*) and 10 negative (e.g., *irritable*) items on a scale from 1 (*Very slightly or not at all*) to 5 (*Extremely*). I averaged items to create measures of positive ($\alpha = .85$) and negative affect ($\alpha = .82$).

Empathy scenarios. Participants rated eight short scenarios (Bruneau, Pluta, & Saxe, 2012) describing various protagonists experiencing physical pain (cutting a finger, catching fingers in a slammed door, scratching a shin, and stepping barefoot on a thumb tack) or social pain (father passing away, getting rejected from college, disapproval after a bad sports performance, overhearing being disliked). Half of the protagonists had female names. Scenario order was randomized for each participant. For each scenario, I measured *perceived pain* in the scenario protagonists with two measures. First, participants rated the pain of each protagonist using a scale from 1 (*No pain at all*) to 5 (*Worst possible pain*). Second, participants rated how much each protagonist felt *hurt*, *wounded*, and *pained* (Buckley, Winkel, & Leary, 2004) on a scale from 1 (*Not at all*) to 5 (*Extremely*). I averaged items to create perceived hurt feeling measures across physical ($.89 \leq \alpha \leq .94$) and social pain scenarios ($.82 \leq \alpha \leq .83$). Both pain ratings correlated highly within each scenario type, $r_{s(76)} \geq .61$, $ps > .001$. I standardized and averaged these measures into indices of perceived physical and social pain.

Participants also rated their *personal distress* when reading each scenario. On a scale from 1 (*Not at all*) to 5 (*Extremely*), participants rated the extent to which they felt *uncomfortable*, *pained*, *bothered*, *unpleasant*, *distress*, as well as *wanted to cringe* while imagining the feelings of each scenario protagonist. I averaged items to create personal distress measures across physical ($.95 \leq \alpha \leq .96$) and social pain scenarios ($.90 \leq \alpha \leq .94$).

Results and Discussion

Preliminary analyses

Participants were not able to identify whether they had taken acetaminophen or placebo, Pearson's $\chi^2(1, N = 80) = 0.00, p = 1.00$.

Aggregating measures of perceived pain, personal distress, and empathic concern across scenario type (physical pain, social pain) assumes that the effect of acetaminophen on these measures does not differ across the individual scenarios. To confirm this assumption, I conducted mixed Analyses of Variances (ANOVAs) with drug condition as between-subjects factor and individual scenario as within-subjects factor. The drug condition \times scenario interaction did not significantly predict perceived pain and personal distress in response to physical pain scenarios, $F(3,228) \leq 1.13, ps \geq .34, \eta_p^2 \leq .02$, or social pain scenarios, $F(3,228) \leq 2.41, ps \geq .07, \eta_p^2 \leq .03$. The drug condition \times scenario interaction approached significance when predicting personal distress while witnessing social pain ($p = .07$), indicating that the effect of acetaminophen on personal distress depended on the scenarios. However, acetaminophen relative to placebo affected personal distress in the same direction across the different scenarios. As a consequence, I averaged personal distress ratings even in this case.

Main analyses

Table 1 displays the effects of acetaminophen relative to the placebo condition on measures of general affect and empathy. As predicted, acetaminophen reduced perceived pain and personal distress when reading scenarios about people in both physical and

Table 1. General Affect and Empathy Scenario Measures by Drug Condition (Experiment 1).

Dependent Variable	Acetaminophen		Placebo		<i>F</i>	η_p^2
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
<i>General Affect^a</i>						
Positive Affect	2.14	0.65	2.21	0.70	0.19	.00
Negative Affect	1.62	0.62	1.42	0.44	2.55	.03
<i>Physical Pain Scenarios</i>						
Perceived Pain	-0.22	1.00	0.22	0.82	4.66*	.06
Personal Distress	2.15	0.89	2.75	1.01	7.68**	.09
<i>Social Pain Scenarios</i>						
Perceived Pain	-0.19	1.01	0.19	0.74	3.49 [†]	.04
Personal Distress	2.00	0.78	2.45	0.85	5.92*	.07

Notes. *dfs* = 1,76. ^a *dfs* = 1,72; due to a programming oversight, I lost the PANAS data of my first four participants.

** $p < .01$, * $p < .05$, [†] $p = .07$

social pain; the effect of acetaminophen on perceived social pain was marginally significant. Furthermore, acetaminophen did not significantly affect general positive or negative affect. Thus, acetaminophen's effects on empathic affect and cognition cannot be attributed to flattened mood.

These findings are the first to show that a pharmacological manipulation of pain responsiveness influences empathy to the pain of others, thus confirming that pain and empathy for pain share a fundamental neurochemical process. However, I tested the effect of acetaminophen in the context of hypothetical scenarios, not when witnessing an actual painful event. The next experiment addressed this issue.

Chapter 3: Extending the Effect of Acetaminophen on Reduced Empathy

To establish the robustness of the effect of acetaminophen on reduced empathy, I replicated and extended the findings of Experiment 1 in a second experiment. As in the previous experiment, I tested the effect of acetaminophen on empathic affect and cognition when reading hypothetical vignettes describing people in physical pain or social pain. Participants in the second experiments also got to know other study participants, two of whom ostensibly ostracized a third participant during a virtual ball-tossing game called *Cyberball* (Williams & Jarvis, 2006). This game allowed testing the effect of acetaminophen on empathy in response to an actual event. As in the previous experiment, I tested the effect of acetaminophen on perceived pain and personal distress when faced with another's pain. I additionally tested the effect of acetaminophen on empathic concern for the other person as another measure of empathic affect. Furthermore, I explored two explanations for the effect of acetaminophen on empathy. As in Experiment 1, I tested whether acetaminophen's effects are due to flattened general positive and negative affect. In Experiment 2, I also tested whether acetaminophen reduces empathy because acetaminophen makes empathy-arousing events appear less negative, a possibility suggested by past research (Durso et al., 2015). Finally, I meta-analytically integrated findings across experiments, to test whether acetaminophen

reduced perceived pain, personal distress, and empathic concern independent of sample and pain modality.

Methods

Participants

One hundred fourteen undergraduate students (48 females; $M_{\text{age}} = 18.8$, $SD = 1.31$; 83 Whites, 12 Asian-Americans, 7 African-Americans, 12 mixed race/others) participated for partial course credit toward their introductory psychology requirement. Two participants failed to finish the study. Nevertheless, I retained the data of these participants in my analyses unless they had failed to provide responses on a dependent measure of interest in a specific set of analyses. In this case, I dropped participants from these analyses. A power-analysis in G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009) based on a power criterion of $(1-\beta)=.80$ and effect sizes obtained in Experiment 1 (see Chapter 2) indicated that a mean cell size of $N=54$ was sufficient to replicate significant findings in Experiment 2. In addition to this power analysis, we took sample attrition into account when predetermining the sample size of Experiment 2.

Pharmacological Procedures

Pharmacological procedures in Experiment 2 were identical to Experiment 1. After signing up for the experiment, participants received an email informing them about the risk factors associated with acetaminophen (see *Appendix A*) and asked them to refrain from participation if they met any of these risk factors and from consuming food for three hours before the experiment.

Upon arrival, participants were randomly assigned to consume a liquid containing 1000mg acetaminophen ($n = 59$) or a placebo ($n = 55$). The experimenter then led participants to individual cubicles. After 60 minutes I administered measures of general affect and empathy. After completing these measures, participants guessed whether they had received acetaminophen or the placebo. Before participants left, the experimenter reminded them to refrain from taking acetaminophen or drinking more than two alcoholic beverages in the upcoming 15 hours.

Measures

General affect. As in Experiment 1, participants completed the PANAS (Watson et al., 1988) as a measure of general affect. I averaged items to create positive ($\alpha = .89$) and negative ($\alpha = .74$) affect measures.

Furthermore, I used two different paradigms to test for the effect of acetaminophen on empathy. First, participants completed a similar version of the hypothetical scenario measure used in Experiment 1. Second, I measured empathic responses when witnessing an actual incidence of social pain.

Empathy scenarios. Participants read the same eight physical and social pain empathy scenarios as in Experiment 1. After reading each scenario, participants rated *perceived pain* of the protagonist, using a scale from -4 (*Worst possible pain*) to +4 (*Most possible pleasure*). I reverse-coded participant's ratings, so higher ratings reflected more empathy for pain. Using the same measure as in Experiment 1, participants rated their *personal distress* while reading each of the physical and social pain scenarios. I averaged items to create personal distress measures for physical ($\alpha = .93$) and social pain

scenarios ($.91 \leq \alpha \leq .93$). Extending the measurement of empathy in Experiment 1, participants rated their *empathic concern* while reading each pain scenario, using an established scale (Batson, Klein, Highberger, & Shaw, 1995). On six items, participants indicated the extent to which they felt empathic concern (e.g., *sympathetic*, *compassionate*), using a scale from 1 (*Not at all*) to 5 (*Extremely*). I averaged items to create empathic concern scales for physical ($.82 \leq \alpha \leq .87$) and social pain scenarios ($.83 \leq \alpha \leq .86$).

Cyberball. To measure empathy in response to actual social pain, participants completed another, well-established paradigm (Masten, Morelli, & Eisenberger, 2011; Meyer et al., 2012; Wesselmann, Bagg, & Williams, 2009). In About 45 min into the study, participants gathered in a large room where they engaged for 15 min in a relationship closeness induction task (Sedikides, Campbell, Reader, & Elliot, 1999). The experimenter asked participants to get to know each other, using a list of provided questions (e.g., *Where are you from?*). This task was intended to make subsequent tasks involving other study participants more relevant. After completing the empathy scenario measures, participants watched two other study participants ostracize a third participant during a virtual ball-tossing game, called *Cyberball* (Williams & Jarvis, 2006). In fact, the computer simulated the players, who tossed the ball to each other for 60 rounds. After the third round, two players ostracized the third player for the rest of the game, not tossing the ball to this player anymore. The identity of the Cyberball players was not disclosed to participants, to ensure that the previous interaction with the other study participants and their characteristics (e.g., their gender) did not influence participants'

response when witnessing the ostracism. After the game, participants completed measures of empathy for each of the three players.

I used the same measures as in Experiment 1 to measure perceived pain in each of the three players. Participants rated the extent to which each player experienced pain and hurt feelings during the game. I averaged hurt feelings items to create a perceived hurt feelings measure for each player ($.82 \leq \alpha \leq .91$). Pain and hurt feelings ratings correlated, $r(112)s \geq .36, ps < .001$. I standardized and averaged these ratings separately for each player, to create measures of perceived social pain. Using the same items as in response to the empathy scenarios, participants rated the extent to which they felt *personal distress* and *empathic concern* while imagining how each of the three players must have felt during the game. For each player rated, I averaged items to create personal distress ($.89 \leq \alpha \leq .94$) and empathic concern scales ($.89 \leq \alpha \leq .92$).

Finally, participants completed an established measure of *perceived negativity* (Berntson et al., 2011; Durso et al., 2015) after each empathy scenario and after watching the Cyberball game. On a scale from -5 (*Extremely negative*) to +5 (*Extremely positive*), participants rated the extent to which each scenario as well as the events during the game was positive or negative. I averaged ratings across physical and across social pain scenarios.

Results

Preliminary analyses

Unlike in Experiment 1, some participants were able to identify whether they had taken acetaminophen or placebo, Pearson's $\chi^2(1, N = 114) = 6.49, p < .05$. However,

controlling for perceived drug consumption did not affect results, except weakening the effect of acetaminophen on perceived pain of the ostracized Cyberball player, from $p = .04$ to $p = .09$.

As in Experiment 1, I ascertained that effects of acetaminophen on empathy measures did not differ across the individual scenarios. Mixed ANOVAs with drug condition as between-subjects factor and individual scenario as within-subjects factor confirmed that assumption, showing that the drug condition \times scenario interaction did not significantly predict perceived pain, personal distress, or empathic concern in response to physical pain scenarios, $F(3,336)s \leq 1.86$, $ps \geq .14$, $\eta_p^2 \leq .02$, or social pain scenarios, $F(3,336)s \leq 1.15$, $ps \geq .33$, $\eta_p^2 \leq .01$.

Main analyses

Table 2 displays effects of acetaminophen relative to the placebo condition on general affect and empathic responses in the scenario measures. Replicating Experiment 1, acetaminophen reduced personal distress when confronted with physical and social pain. Unlike in Experiment 1, acetaminophen did not significantly decrease perceived physical or social pain. In addition, I extended findings of Experiment 1 to other-focused empathic affect; acetaminophen also reduced empathic concern towards others depicted in physical or social pain.

Furthermore, Experiment 2 showed that acetaminophen not only reduces empathy to hypothetical scenarios, but also to an actual incident of social pain. *Table 3* depicts effects of acetaminophen relative to placebo on the Cyberball empathy measures separately for each Cyberball player. As expected, acetaminophen reduced perceived

pain, empathic concern, and personal distress (marginally) when witnessing ostracism. As predicted, this effect was restricted to the ostracized victim; acetaminophen did not significantly reduce empathy towards the ostracism perpetrators.

Replicating Experiment 1, acetaminophen did not change positive or negative affect (see *Table 2*), which is further evidence that acetaminophen does not exert its effect on empathy through flattened mood. Finally, controlling for perceived negativity of the empathy scenarios or the events during the Cyberball game did not diminish effects of acetaminophen on empathy (see *Tables 4 and 5*), suggesting that acetaminophen does not affect empathy through making the pain of others appear less negative in general.

Meta-Analytic Integration

Because effects of acetaminophen on empathic affect and cognition were not always significant, I conducted a *fixed-effects* meta-analysis, adjusting effect sizes for multiple measurements of empathic affect and cognition within a sample (Borenstein, Hedges, Higgins, & Rothstein, 2009). I did not conduct a *random-effects* meta-analysis, as it is often recommended (Borenstein et al., 2009) because two reasons: First, the number of studies in the meta-analysis was too small to allow a meaningful estimation of random effects, and, second, my goal was to estimate effect sizes across my studies, not to make a generalizing claim about the true size of my effects. I tested whether acetaminophen reduced perceived pain, personal distress, and empathic concern towards others' pain, independent from pain modality and across experiments. As hypothesized, acetaminophen relative to placebo decreased personal distress in response to others' pain, Hedge's $g = 0.49$, $z = 3.86$, $p < 0.001$, with a 95% confidence interval ranging from 0.24

Table 2. General Affect and Empathy Scenario Measures by Drug Condition (Experiment 2).

Dependent Variable	Acetaminophen		Placebo		<i>F</i>	η_p^2
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
<i>General Affect</i>						
Positive Affect	2.54	0.71	2.62	0.85	0.32	.00
Negative Affect	1.27	0.33	1.27	0.36	0.00	.00
<i>Physical Pain Scenarios</i>						
Perceived Pain	2.70	0.67	2.55	1.05	0.83	.01
Personal Distress	2.42	0.85	2.94	0.90	9.82**	.08
Empathic Concern	1.68	0.55	2.00	0.74	6.95**	.06
<i>Social Pain Scenarios</i>						
Perceived Pain	2.63	0.75	2.58	0.90	0.09	.00
Personal Distress	2.26	0.77	2.57	0.86	3.95*	.03
Empathic Concern	2.04	0.66	2.31	0.76	4.07*	.04

Note. *dfs* = 1,112.

** $p < .01$, * $p < .05$

to 0.74, and empathic concern for others in pain, Hedge's $g = 0.44$, $z = 2.60$, $p < 0.01$, with a 95% confidence interval ranging from 0.11 to 0.77. The effect on reduced perceived pain in others was marginal significant, Hedge's $g = 0.18$, $z = 1.70$, $p = 0.09$, with a 95% confidence interval ranging from -.028 to 0.39, suggesting that the effect of acetaminophen on empathic cognition is weak.

Discussion

Experiment 2 replicated and extended the findings of Experiment 1. As in the previous experiment, acetaminophen reduced personal distress when reading hypothetical scenarios depicting people in physical or social pain. Unlike Experiment 1,

Table 3. Cyberball Empathy Measures by Drug Condition (Experiment 2).

Dependent Variable	Acetaminophen		Placebo		<i>F</i>	η_p^2
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
<i>Ostracized Player</i>						
Perceived Pain	-0.17	0.99	0.19	0.87	4.20*	.04
Personal Distress	2.25	0.98	2.61	1.01	3.70 [†]	.03
Empathic Concern	1.68	0.74	2.05	0.92	5.73*	.05
<i>Included First Player</i>						
Perceived Pain	-0.06	0.61	0.06	1.00	0.63	.01
Personal Distress	1.24	0.47	1.34	0.61	1.00	.01
Empathic Concern	1.08	0.29	1.14	0.37	0.77	.01
<i>Included Second Player</i>						
Perceived Pain	-0.04	0.80	0.04	1.06	0.23	.00
Personal Distress	1.22	0.34	1.38	0.56	3.34 [†]	.03
Empathic Concern	1.08	0.23	1.13	0.31	0.78	.01

Note. *dfs* = 1,112.

* $p < .05$, [†] $p < .07$

acetaminophen did not change perceived pain when reading hypothetical scenarios about physical or social pain. Furthermore, Experiment 2 extended the Experiment 1, showing that acetaminophen also decreased empathic concern when reading about the pains of others. Finally, Experiment 2 showed that acetaminophen reduced perceived pain, (marginally) personal distress, and empathic concern to an actual incident of social pain, specifically when witnessing ostracism during a virtual ball-tossing game, *Cyberball* (Williams & Jarvis, 2006).

I also tested whether manipulating pain responsiveness affects different aspects of empathy. In contrast to the effects of acetaminophen on personal distress and empathic concern, the effect on perceived pain was inconsistent across experiments. A meta-

Table 4. Acetaminophen vs. Placebo Condition Predicting Scenario Empathy with and without Controlling for Perceived Scenario Negativity (Experiment 2).

Dependent Variable	w/o Negativity ^a		w/ Negativity ^b	
	<i>F</i>	η_p^2	<i>F</i>	η_p^2
<i>Physical Pain Scenarios</i>				
Perceived Pain	0.83	.01	1.94	.02
Personal Distress	9.82**	.08	9.47**	.08
Empathic Concern	6.95**	.06	6.59*	.06
<i>Social Pain Scenarios</i>				
Perceived Pain	0.09	.00	0.05	.00
Personal Distress	3.95*	.03	4.36*	.04
Empathic Concern	4.07*	.04	4.04*	.04

Notes. ^a *dfs* = 1,112. ^b *dfs* = 1,110.

*** $p < .001$, ** $p < .01$, * $p < .05$

analysis across samples and pain modalities showed that acetaminophen marginally reduced perceived pain, in addition to personal distress and empathic concern when witnessing others in pain. An inspection of effect sizes suggested moderate effects of acetaminophen on empathic affect measures, and a small effect of acetaminophen on empathic cognition (Cohen, 1988). However, a larger number of studies integrated across a random-effects meta-analysis (Borenstein et al., 2009) is necessary to make claims about the true size of the effect of acetaminophen on empathic affect and cognition.

Finally, I explored two explanations for the effect of acetaminophen on empathy. In both experiments, acetaminophen failed to affect general positive or negative affect,

Table 5. Acetaminophen vs. Placebo Condition Predicting Cyberball Empathy with and without Controlling for Perceived Cyberball Negativity (Experiment 2).

Dependent Variable	w/o Negativity ^a		w/ Negativity ^b	
	<i>F</i>	η_p^2	<i>F</i>	η_p^2
<i>Ostracized Player</i>				
Perceived Pain ^c	4.20*	.04	3.37 [†]	.03
Personal Distress	3.70 [†]	.03	2.98 [†]	.03
Empathic Concern	5.73*	.05	5.83*	.05
<i>Included First Player</i>				
Perceived Pain	0.63	.01	0.91	.01
Personal Distress	1.00	.01	0.28	.00
Empathic Concern	0.77	.01	0.87	.01
<i>Included Second Player</i>				
Perceived Pain	0.23	.00	0.42	.00
Personal Distress ^c	3.34 [†]	.03	2.09	.02
Empathic Concern	0.78	.01	0.84	.01

Notes. ^a *dfs* = 1,112. ^b *dfs* = 1,110. ^c The drop to marginal significance was not significant, as a bias-corrected 95% confidence interval resulting from a bootstrapping test drawing 5000 test samples indicated, [-.06, .13]. ^d The drop to non-significance was not significant, as a bias-corrected 95% confidence interval resulting from a bootstrapping test drawing 5000 test samples indicated, [-.02, .07].

* $p < .05$, [†] $p \leq .07$

suggesting that flattened mood did not account for my findings. In Experiment 2, blunted perceived negativity of empathy-arousing events also failed to explain acetaminophen's effects on empathic affect and cognition. These analyses suggest that the effects of

acetaminophen on empathy are not due to a general mechanism of mood or perceived negativity.

This research extends knowledge of the cognitive and affective effects of acetaminophen (DeWall et al., 2010; Durso et al., 2015; Randles et al., 2013), showing that acetaminophen has important psychosocial side effects, specifically on the cognitive and emotional responsiveness to other people's pain. This finding suggests that the social consequences of acetaminophen could be far more costly than previously assumed, given how many people consume acetaminophen on a regular basis (Kaufman et al., 2002). For example, acetaminophen may contribute to widespread social problems related to a lack of empathy, such as increased aggressive behavior (Jolliffe & Farrington, 2004; Miller & Eisenberg, 1988; Vachon et al., 2014). I tested this hypothesis in a second set of experiments, partially relying on data not previously reported in Experiments 1 and 2 (see Chapters 2 and 3).

Chapter 4: Establishing the Effect of Acetaminophen on Increased Aggression

The effect of acetaminophen on reduced empathy suggests that acetaminophen may also increase the willingness to inflict pain on other people. I thus established the effect of acetaminophen on increased aggression in a first experiment. To measure aggressive behavior, I used an well-validated measure, a modified version of the Taylor Aggression Paradigm (Bushman & Baumeister, 1998; Taylor, 1967).

Methods

Participants

Sixty undergraduate students from The Ohio State University (26 females; $M_{\text{age}} = 18.9$, $SD = 1.21$; 48 Whites, 3 Asian-Americans, 2 African-Americans, 7 mixed race/others) participated for partial course credit toward their introductory psychology requirement. Eight participants did not complete the aggression measure and one participant dropped out in the beginning of the study. Similar to Experiment 1 (see Chapter 2), I determined sample size based on previous research which indicated a sample size between 30-50 participants per cell was sufficient to provide sufficient power to detect a behavioral effect of acetaminophen (Durso et al., 2015).

Pharmacological Procedures

Pharmacological procedures in Experiment 3 were similar to the previous experiments. After signing up for the experiment, participants received an email

informing them about the risk factors associated with acetaminophen (see *Appendix A*) and asked them to refrain from participation if they met any of these risk factors and from consuming food for three hours before the experiment.

Upon arrival, participants were randomly assigned to either consume two 500 mg acetaminophen pills ($n = 22$) or two identical placebo pills ($n = 29$). The experimenter then led participants to individual cubicles. About 90 minutes after drug administration, participants completed the aggression task. Afterwards, participants guessed whether they had received acetaminophen or the placebo. Before participants left, the experimenter reminded them to refrain from taking acetaminophen or drinking more than two alcoholic beverages in the upcoming 15 hours.

Aggression Measure

While completing the aggression measure (Bushman & Baumeister, 1998; Taylor, 1967), participants competed against an opponent in 10 trials to see who could respond to a visual cue faster, with the loser receiving a blast of white noise through headphones. In the beginning of each trial, participants selected the volume and duration for each blast. Volume levels ranged from 60 dB (Level 1) to 105 dB (Level 10). A no noise level (Level 0) was also provided. Duration level ranged from 0 to 5 sec in 0.5 sec increments. At the end of each trial, participants received feedback about the noise volume and duration their opponent had selected for them. Although led to believe they were competing against another person, participants were actually playing against the computer and the order of wins and losses during the game was predetermined. In case participants responded slowly to the visual cue (> 750 ms), they automatically lost the

trial. The order of wins and losses across trials was the same for each participant (loss, loss, win, win, loss, win, loss, win, win, loss), as were the opponent's volume (85, 80, 95, 105, 105, 85, 75, 80, 65, 60 dB) and duration selection (3, 4, 1.5, 3, 3, 1, 3.5, 2.5, 2, 0.5 sec). The opponent was designed to starkly increase and then to decrease in aggressive behavior over the course of the task, to provide participants reason for a retaliatory aggressive response.

Results and Discussion

Statistical Procedures

For each aggression task trial, I averaged volume and duration selections for both participants and opponents to create an indicator of aggressive behavior. Because aggression trials over time were nested within participants, the data had a hierarchical and longitudinal structure. As a consequence, I used mixed modeling growth curve analyses to test the effect of acetaminophen on aggression using the MIXED command in SPSS (Peugh & Enders, 2005). This approach allowed to model non-linear patterns in aggressive behavior across time. I modeled the residual covariance structure of the data by imposing a heterogeneous first-order autoregressive residual covariance structure, to allow for residual error variances to vary between trials and to account for declining residual error covariances across trials as a function of increased trial distance. As recommended (Peugh & Enders, 2005), I grand-mean centered predictors in all our analyses. Furthermore, I calculated fixed and random coefficients using restricted maximum likelihood estimation. Finally, I calculated partial correlations as indicators of effect size (Rosnow & Rosenthal, 1996).

Preliminary Analyses

Participants were not able to identify above chance whether they had consumed acetaminophen or the placebo, Pearson's $\chi^2(1, N = 51) = 0.38, p = .54$. Furthermore, a visual inspection of participants' aggressive behavior across the 10 trials revealed a negative quadratic trend (see *Figure 1*), suggesting that participants, as expected, matched their aggressive behavior to the aggressive behavior of their opponent (Axelrod, 1984; Rapoport & Chammah, 1965). A longitudinal growth analysis (Peugh & Enders, 2005) testing a quadratic trend in aggressive behavior over time confirmed that observation, $pr = -.20, t(298) = -3.53, p < .001$. Drug condition did not moderate this trend, $pr = .03, t(287) = 0.51, p = .61$. I modeled the negative quadratic trend in aggressive behavior in all subsequent mixed models of Experiment 3 by including a quadratic time variable as predictor.

Main Analyses

Figure 1 depicts the effect of acetaminophen on aggressive behavior across the 10 aggression task trials. As hypothesized, acetaminophen relative to placebo increased aggressive behavior, $pr = -.32, t(104) = -3.38, p < .01$.

This finding provided first evidence that consuming acetaminophen increases aggressive behavior. However, it remained unclear whether acetaminophen increases aggressive behavior for everybody, or whether individual difference factors attenuate the effect of acetaminophen on increased aggression. Indeed, dispositional empathy predicts reduced aggressive behavior (Jolliffe & Farrington, 2004; Miller & Eisenberg, 1988; Vachon et al., 2014), suggesting that people high on dispositional empathic traits may be

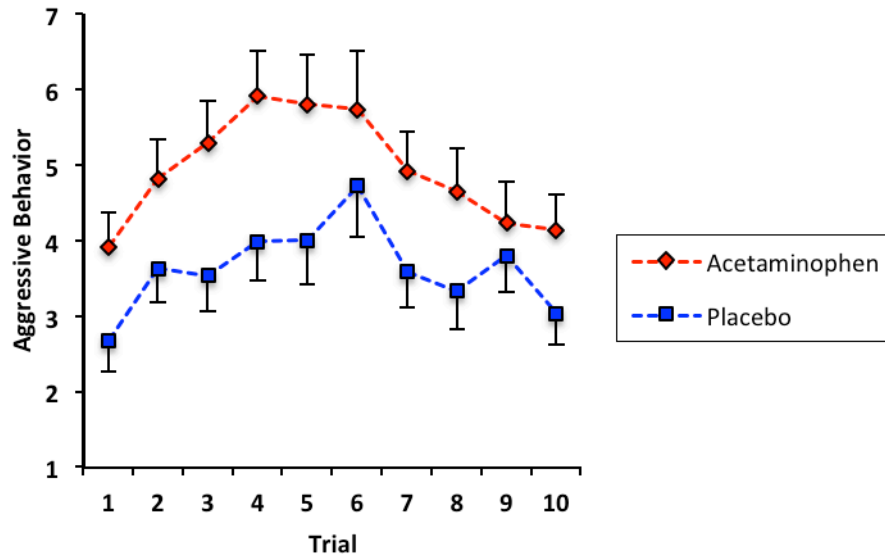


Figure 1. Means and standard errors of acetaminophen and placebo conditions predicting aggressive behavior (Experiment 3).

less susceptible to the effect of acetaminophen. I addressed this issue using data from Experiments 1 and 2 (see Chapters 2 and 3) not previously reported.

Chapter 5: Empathic Concern Moderating the Effect of Acetaminophen on Increased Aggression

Next, I examined whether dispositional empathic traits attenuated the effect of acetaminophen on aggressive behavior, because people high on dispositional empathy show less aggression (Jolliffe & Farrington, 2004; Miller & Eisenberg, 1988; Vachon et al., 2014). Specifically, I tested the moderating role of dispositional affective and cognitive empathy (Davis, 1983; Lawrence et al., 2004; Mehrabian & Epstein, 1972), using data from Experiment 1 (see Chapter 2) not previously reported. In addition to measures affect and empathy, participants of Experiment 1 also completed a measure of dispositional empathy (Davis, 1983), and the same aggression measure as in Experiment 3 (Bushman & Baumeister, 1998; Taylor, 1967).

Methods

Participants and Pharmacological Procedures

For details on sample size, the demographic composition of the sample, sample drop out during the experiment, and pharmacological procedures, see Chapter 2. Eighty participants were randomly assigned to consume a liquid containing 1000mg acetaminophen ($n=40$) or a placebo ($n=40$).

Measures

Dispositional empathy. After drug administration, participants completed an established measure of dispositional empathy, the IRI (Davis, 1983). The IRI treats empathy as a dispositional four-dimensional construct. On 5-point scales (0 = *Does not describe me very well*, 4 = *Describes me very well*), the perspective-taking subscale measures the disposition to take the perspective of others, the fantasizing subscale measures the disposition to imagine oneself as fictitious characters, the personal distress subscale measures the disposition to experience distress in difficult social situations, and the empathic concern subscale measures the disposition to empathize with the distress of other people. Sample items include ‘*I try to look at everybody's side of a disagreement before I make a decision*’ for the perspective taking subscale ($\alpha = .79$), ‘*I really get involved with the feelings of the characters in a novel*’ for the fantasizing subscale ($\alpha = .78$), ‘*In emergency situations, I feel apprehensive and ill-at-ease*’ for the personal distress subscale ($\alpha = .72$), and ‘*I often have tender, concerned feelings for people less fortunate than me*’ for the empathic concern subscale ($\alpha = .75$).

Aggression. About 75 minutes after acetaminophen consumption, participants completed the same version of the Taylor Aggression Paradigm (Bushman & Baumeister, 1998; Taylor, 1967) as in Experiment 3. Again, I conducted longitudinal growth analyses (Peugh & Enders, 2005) to analyze participants’ aggressive responses across the 10 trials of the aggression task.

Results and Discussion

Preliminary Analyses

As in the previous experiment, a visual inspection showed a negative quadratic trend in aggressive behavior across the 10 trials (see *Figure 2*). A longitudinal growth analysis (Peugh & Enders, 2005) confirmed that trend, $pr = -.14$, $t(389) = -2.75$, $p < .01$. Drug condition did not moderate this trend, $pr = -.07$, $t(384) = -1.38$, $p = .17$. Again, I modeled the negative quadratic trend in aggressive behavior in all subsequent analyses of Experiment 4 by including a quadratic time variable as predictor.

Main Analyses

Figure 2 depicts the effect of acetaminophen on aggressive behavior across the 10 aggression task trials. Acetaminophen relative to placebo marginally increased aggressive behavior, $pr = -.14$, $t(152) = -1.78$, $p = .08$.

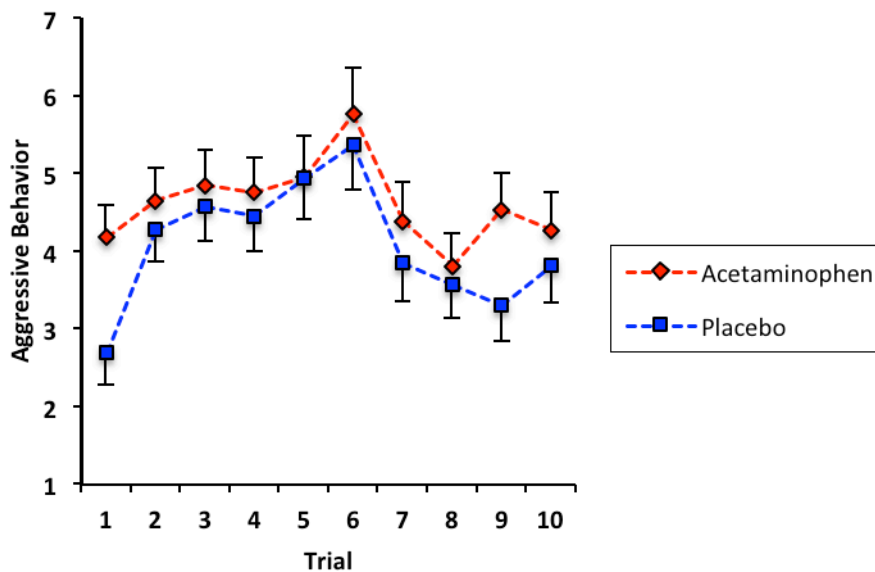


Figure 2. Means and standard errors of acetaminophen and placebo conditions predicting aggressive behavior (Experiment 4).

Aspects of dispositional empathy moderated this effect. Dispositional empathic concern for the distress of others moderated the effect of acetaminophen relative to placebo on aggressive behavior, $pr = -.18$, $t(152) = -2.24$, $p < .05$ (see *Figure 3*, panel A). Acetaminophen relative to placebo increased aggressive behavior only for people low in dispositional empathic concern, $pr = .21$, $t(152) = 2.63$, $p < .01$, not for people high in dispositional empathic concern, $pr = -.04$, $t(152) = -0.53$, $p = .60$.

In addition, personal distress moderated the effect of acetaminophen on

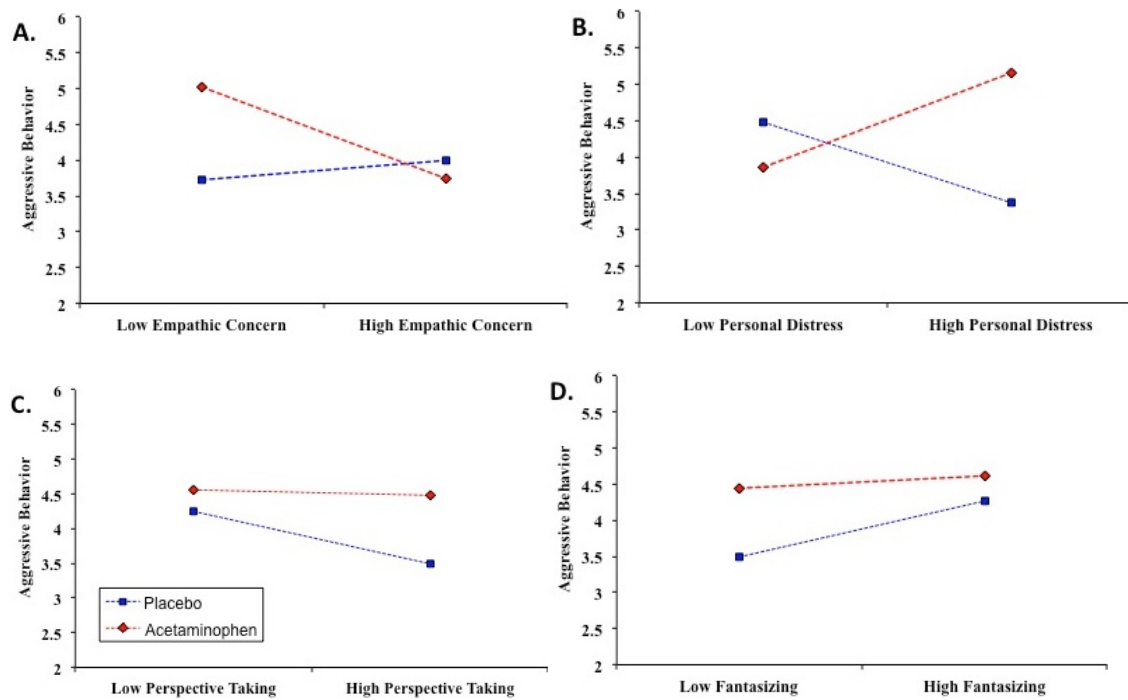


Figure 3. IRI Empathy subscales ($Mean \pm 1 SD$) moderating the effect of acetaminophen relative to placebo conditions on aggressive behavior (Experiment 4).

aggressive behavior relative to placebo, $pr = .28$, $t(154) = 3.67$, $p < .001$ (see *Figure 3*, panel B). Acetaminophen relative to placebo increased aggressive behavior for people high in personal distress, $pr = .30$, $t(154) = 3.86$, $p < .001$, not for people low in dispositional personal distress, $pr = -.11$, $t(152) = -1.36$, $p = .18$. Neither perspective-taking nor fantasizing moderated the effect of acetaminophen on aggressive behavior, $|prs| \leq .08$, $|ts|(150) \leq 0.99$, $ps \geq .33$ (see *Figure 3*, panels C and D).

These analyses indicated acetaminophen does not increase aggressive behavior in all people. Specifically, for people high in dispositional empathic concern, acetaminophen has no significant effect on increased aggressive behavior, suggesting that acetaminophen does not interfere with the ability of people to control aggression when they care about how their behavior affects the well-being of other people. However, I did not predict this finding, so it needed replication. Furthermore, it remains unclear whether provocation could exacerbate the effect of acetaminophen on increased aggressive behavior. Data previously not reported in Experiment 2 (see Chapter 3) and a re-analysis of all data involving the effect of acetaminophen on aggressive behavior addressed these questions.

Chapter 6: Further Exploring the Effect of Acetaminophen on Increased Aggressive Behavior

To explore the robustness of the moderating role of high empathic concern in attenuating the effect of acetaminophen on increased aggressive behavior, I used data from Experiment 2 (see Chapter 3) not previously reported. In addition to measures of affect and empathy, participants also had completed a measure of dispositional empathy (Davis, 1983) and of aggressive behavior (Bushman & Baumeister, 1998; Taylor, 1967). Furthermore, I explored whether acetaminophen increased aggressive behavior particularly after interpersonal provocation. I addressed the latter question by re-analyzing all experiments on the effect of acetaminophen on increased aggressive behavior.

Methods

Participants and Pharmacological Procedure

For details on sample size, the demographic composition of the sample, sample drop out during the experiment, and pharmacological procedures, see Chapter 3. One hundred fourteen participants were randomly assigned to consume a liquid containing 1000mg acetaminophen ($n=59$) or a placebo ($n=55$).

Measures

As in Experiment 2 (see Chapter 5), participants completed the perspective taking ($\alpha = .79$), fantasizing ($\alpha = .81$), personal distress ($\alpha = .74$), and empathic concern ($\alpha = .82$) subscales of the IRI (Davis, 1983) after drug administration. About 75 minutes later, participants completed the same version of the Taylor aggression paradigm as in Experiments 1 and 2 (Bushman & Baumeister, 1998; Taylor, 1967; see Chapters 4 and 5). Again, I analyzed aggressive responses over the 10 trials of this task, using mixed modeling longitudinal growth analyses (Peugh & Enders, 2005).

Results

Preliminary Analyses

Some participants were able to identify above chance, whether they had consumed acetaminophen or placebo, Pearson's $\chi^2(1, N = 112) = 6.08, p < .05$. However, controlling for perceived drug consumption did not affect results in this experiment.

As in Experiment 1 and 2, a visual inspection of participant's aggressive responses across 10 trials indicated a negative quadratic trend (see *Figure 4*), $pr = -.18, t(677) = -4.76, p < .001$. Drug condition did not moderate this trend, $pr = -.03, t(677) = -0.99, p = .32$. Again, I modeled this quadratic aggressive response pattern in all subsequent mixed models of Experiment 5 by including a quadratic time variable as predictor.

Main Analyses

Figure 4 depicts the effect of acetaminophen on aggressive behavior across the 10 aggression task trials. There was no main effect of acetaminophen on aggressive behavior, $pr = -.05, t(210) = -0.75, p = .45$. However, replicating Experiment 2,

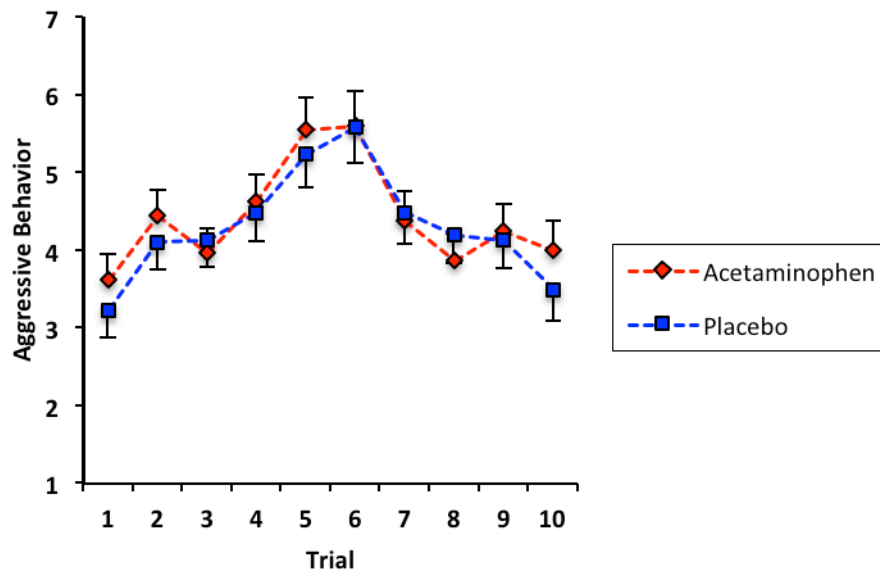


Figure 4. Means and standard errors of acetaminophen and placebo conditions predicting aggressive behavior (Experiment 5).

dispositional empathic concern (and, additionally, fantasizing) attenuated the effect of acetaminophen on aggressive behavior across 10 trials of the aggression task, $pr = -.20$, $t(216) = -3.04$, $p < .01$ (see *Figure 5*, panel A). Again, acetaminophen relative to placebo increased aggressive behavior only for people low in dispositional empathic concern, $pr = .19$, $t(216) = 2.84$, $p < .01$, not for people high in dispositional empathic concern, $pr = -.07$, $t(216) = 0.97$, $p = .33$. In addition, fantasizing moderated the effect of acetaminophen relative to placebo on aggressive behavior, $pr = -.17$, $t(212) = -2.44$, $p < .05$ (*Figure 5*, panel D). Acetaminophen relative to placebo marginally increased aggressive behavior for people low in fantasizing, $pr = .13$, $t(212) = 1.89$, $p = .06$, but not for people high in

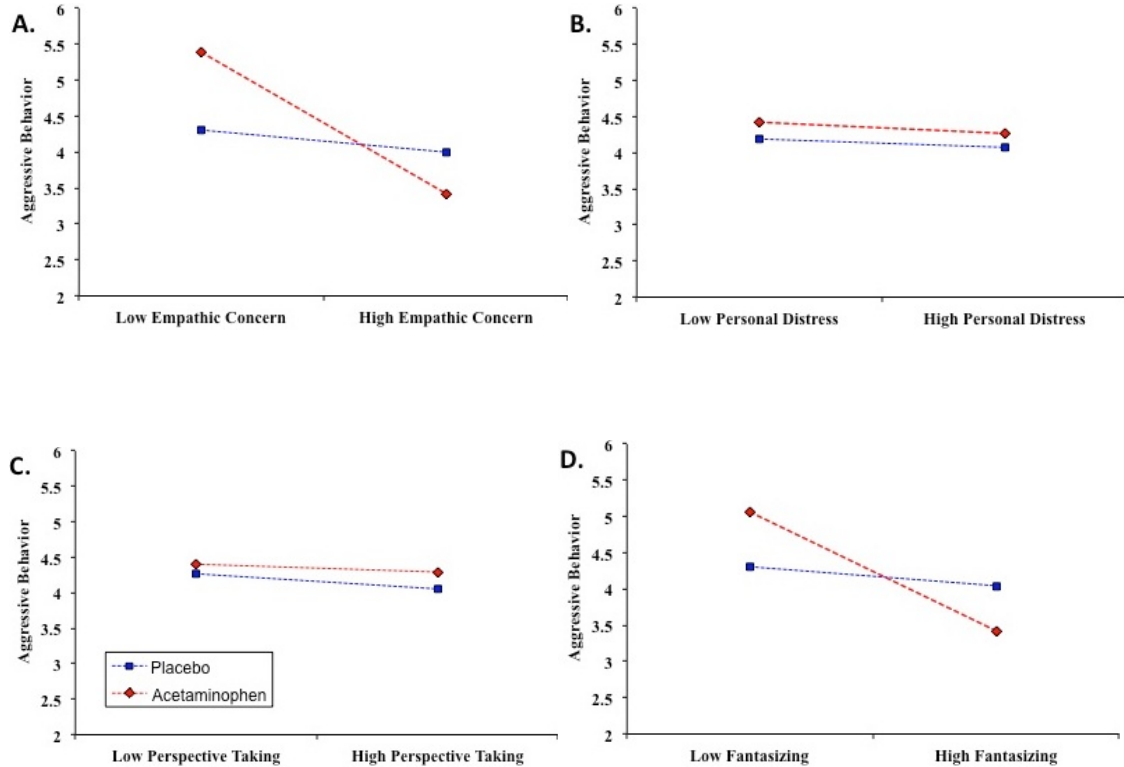


Figure 5. IRI Empathy subscales ($Mean \pm 1 SD$) moderating the effect of acetaminophen relative to placebo conditions on aggressive behavior (Experiment 5).

fantasizing, $pr = -.11$, $t(212) = -1.57$, $p = .12$. Neither personal distress nor perspective taking moderated the effect of acetaminophen on aggressive behavior, $|prs| \leq .01$, $|ts|(207) \leq 0.17$, $ps \geq .86$ (see *Figure 5*, panels B and C).

Re-analyzing the Aggression Data

Finally, I re-analyzed all data on the effect of acetaminophen on aggressive behavior; I explored whether aggression effects of acetaminophen were pronounced after

provocation during the aggression task, i.e., after participants lost a trial, after opponents assigned more aggressive noise-blasts, or – most provoking – after a combination of both.

Analytic Strategy

For each data set, I used a residual change strategy to test change in aggressive behavior from trial to trial, simultaneously regressing participants' trial $n+1$ aggressive behavior on the opponent's aggressive behavior on trial n , competition outcome for the participant on trial n , drug condition, and the two- and three-way interactions between those variables, controlling for participants' trial n aggressive behavior. This approach allowed me to test whether acetaminophen moderated participants' increased aggressive response after provocation.

As in previous mixed modeling analyses, I grand-mean centered predictors in all analyses. Again, I calculated fixed and random coefficients using restricted maximum likelihood estimation and partial correlations as indicators of effect size (Rosnow & Rosenthal, 1996).

Results

Across all experiments, results were consistent with the interpretation that acetaminophen does not increase aggressive behavior in retaliation to provocation during the aggression task. Lagged-trial analyses separately for all three experiments indicated that acetaminophen did not change aggressive behavior after provocation, $|prs| < .03$, $|ts| < 1$, $ps \geq .36$.

Discussion

Again, acetaminophen increased aggressive behavior, except for people high in dispositional empathic concern for the distress of other people. This finding suggests that a dispositional tendency to care for the well-being of others can protect from the influence of acetaminophen on aggressive behavior. However, it remains unclear why dispositional empathic concern attenuated the effect of acetaminophen on aggression. It is possible, though, that people high in empathic concern tend to be motivated to keep harm away from others, either deliberately or in a habitual fashion. Other aspects of dispositional empathy did not consistently moderate the aggression effect of acetaminophen across different experiments. Therefore, I refrain from discussing other moderator effects that I could not replicate because these effects are likely due to Type 1 error or sample idiosyncrasies. Together, results from two experiments suggest that a disposition to experience empathic perception or self-directed empathic affect is not enough to protect from the effect of acetaminophen on aggressive behavior. Apparently, the disposition to care for the fate of others is a driving factor behind the protective effect of dispositional empathy.

Furthermore, a re-analysis of the aggression data showed that increased aggressive behavior after consuming acetaminophen did not depend on interpersonal provocation, a situation in which people are most likely to be aggressive (Anderson & Bushman, 2002; Berkowitz, 1990; Bushman & Huesmann, 2010). This finding suggests that acetaminophen increases a general willingness to inflict pain on other people rather than reactive aggressive behavior. However, more research on the process underlying the effect of acetaminophen on aggression is needed to confirm this interpretation.

Chapter 7: Discussing the Social Side Effects of Acetaminophen

To date, we know very little about how many psychotropic medications, such as acetaminophen, influence social affect, cognition, and behavior. Across three experiments, acetaminophen had important psychosocial side effects. In a first set of experiments, acetaminophen consistently reduced empathic affect and – to a small degree – empathic cognition. Furthermore, I extended these findings to actual social behavior. In a second set of experiments (which included the two previous experiments), acetaminophen also increased aggressive behavior for people low in dispositional empathic concern.

These findings are the first to show that the popular physical painkiller can reduce empathy and increase aggressive behavior. As a consequence, these findings complement but also extend existing theory and research on the psychosocial, neuronal, and neurochemical bases of empathy and aggression, deepening our understanding of how the physical pain system is involved in the regulation of psychosocial processes. This research has several theoretical implications making these findings a unique contribution beyond previous research on empathy and aggression.

Theoretical Implications and Future Directions

First, my findings complement and extend research on the neuroscience of empathy and aggression. Research on the neuronal underpinnings empathy has mostly

centered around two major theoretical frameworks: *Theory of Mind* frameworks suggest that empathy requires the ability to understand another's mental states based on naïve theories about the mind (Baron-Cohen, 1997; Dvash & Shamay-Tsoory, 2014; Frith & Frith, 2003; Premack & Woodruff, 1978; Saxe, 2009; Singer, 2009; Zaki, 2014), while *shared representation* frameworks suggest that empathy requires the neural simulation of another's feelings, goals, or actions (Decety & Jackson, 2004; Gallese, 2001; Iacoboni, 2009; Preston & De Waal, 2002; Prinz, 1997; Zaki, 2014). In so far as acetaminophen acts primarily on pain-specific neural circuitry, my findings provide first pharmacological evidence suggesting that the experience of empathy for pain relies on the representation of physical pain. In this case, my findings confirm conclusions drawn in previous imaging studies on the neurological overlap of pain and empathy for pain (Lamm et al., 2011). In so far as acetaminophen acts on a more fundamental mechanism unspecific to pain, such as reduced affective salience of self-relevant events (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Seeley et al., 2007) or impaired conflict detection (Botvinick, 2007; Carter & van Veen, 2007), my findings still support a shared process account of pain and empathy for pain. More research is needed on whether this process is pain-specific or not.

Despite theoretical relevance, researchers have rarely applied shared representation frameworks to understand complex social behaviors, such as aggression. These frameworks mostly have been limited to explaining neuronal underpinnings of basic social behavior, such as how mirror neuron mediate the imitation of basic goal-directed action (for selected reviews, see Ferrari, 2012; Iacoboni, 2009; Rizzolatti &

Craighero, 2004). Shared representation frameworks have implicated the neuronal physical pain system in regulating empathy for the pain of others (Decety & Jackson, 2004; Gallese, 2001; Preston & De Waal, 2002; Singer, 2006). However, none of these approaches have explicitly tested whether the physical pain system is involved in regulating whether people actually inflict pain on other people, i.e., in regulating aggressive behavior. In contrast, my findings show that decreasing responsiveness to physical pain can increase aggressive behavior, suggesting that the scope of shared representation frameworks in understanding social behavior is broader than previously assumed. For example, the neuronal pain system may also be involved in the regulation of prosocial behavior, cooperation, and attachment. However, this hypothesis needs further investigation.

Furthermore, these findings extend social-psychological research on the factors contributing to pro- and antisocial cognition, affect, and behavior. Research in the cognitive-neoassociationistic tradition has suggested that pain can decrease empathy and increase aggressive behavior because pain causes negative affect and thus can make anger and aggressive intentions more accessible (Anderson & Bushman, 2002; Berkowitz, 1993). A major source of negative affect and social pain is interpersonal provocation (Bushman & Huesmann, 2010). Given that acetaminophen ameliorates physical and social pain (DeWall et al., 2010), cognitive-neoassociationistic theories predict that acetaminophen relative to placebo decreases anti-social cognition, affect, and behavior, particularly during provocation. In contrast, my findings show that a pharmacological amelioration of physical pain sensitivity increases aggressive behavior,

independent of interpersonal provocation. However, this effect may be due to a more basic cognitive or affective impairment than increased aggressive intentions, such as through reducing susceptibility to threat (Randles et al., 2013; Umathe, Manna, Utturwar, & Jain, 2009) or sensitivity to the harmful consequences of one's actions. Cognitive-neoassociationistic explanations of aggressive behavior do not necessarily apply to these processes. In general, more research is needed to reconcile cognitive-neoassociationistic and shared representation accounts of aggressive behavior.

It is important to note that the pharmacokinetics and behavioral effects of acetaminophen may be different for people in pain compared to people in no pain, which is the sample that I studied. It is possible that acetaminophen decreases aggressive behavior for people in pain instead of increasing aggressive behavior, because acetaminophen reduces pain and consequently aggressive affect and cognition (Anderson & Bushman, 2002; Berkowitz, 1993). More research, for example on populations in chronic pain, is needed to test this possibility.

In addition, these findings suggest that the experience of pain and responsiveness to other's pain share a common neurochemical mechanism. It remains unclear which neurotransmitter system accounts for this neurochemical overlap. However, research suggests that – among others – serotonergic, opioid, cannabinoid, or anti-inflammatory mechanisms may mediate acetaminophen's effects on physical pain responsiveness (Bertolini et al., 2006; Graham et al., 2013; Smith, 2009; Toussaint et al., 2010). Previous research on the neurochemical basis of empathy so far has mostly focused on the intranasal administration of oxytocin, a neuropeptide implicated in social cognition and

prosocial behavior (Bartz, Zaki, Bolger, & Ochsner, 2011). There is tentative evidence that both oxytocin and acetaminophen affect empathy for other's pain through influencing activity in the insula and the cingulate cortex (Bos, Montoya, Hermans, Keyesers, & van Honk, 2015; DeWall et al., 2010). This finding raises the intriguing possibility that intranasal oxytocin and acetaminophen act on interacting, and possibly counteracting, neurochemical systems. Furthermore, research on the neurochemical underpinnings of aggressive behavior has mostly focused on reduced impulse control due to increased testosterone levels (Archer, 1991; Mehta & Beer, 2009) or reduced serotonergic function (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009; Linnoila et al., 1983). In contrast, there is evidence that *increased* serotonin levels mediate acetaminophen's effect on reduced physical pain sensitivity (Courade et al., 2001; Pickering et al., 2006; Pini, Sandrini, & Vitale, 1996). As a consequence, more research is needed to clarify how acetaminophen impacts neurochemical systems to affect cognitive, emotional, and behavioral responsiveness to the pain of other people.

Finally, it is important to note that pharmacologically reducing sensitivity to physical pain did not lead to aggressive behavior in all participants. Specifically, high dispositional empathic concern buffered the effect of acetaminophen on aggressive behavior, which is consistent with previous findings on the effects of dispositional empathy on reduced aggressive behavior (Jolliffe & Farrington, 2004; Miller & Eisenberg, 1988; Vachon et al., 2014), as well as with recent approaches on how personal factors modify other neurochemical processes (Bartz et al., 2011). Neurochemical

interventions do not act in isolation but within a psychosocial context. My findings are consistent with that idea.

Policy Implications

These findings have significant public health implications because many people consume acetaminophen on a weekly basis (Kaufman et al., 2002). Current pharmacological theory and research is based on a main-effects paradigm, assuming that psychoactive drugs operate similarly across people and contexts and focusing mostly on the physiological and basic psychological effects of these drugs. In contrast, social neurochemical research (Bartz et al., 2011) suggests that psychosocial factors can modify neurochemical interventions and that neurochemical interventions can influence psychosocial processes beyond altering mere physiology and basic psychology. There are probably complex and reciprocal effects between most psychoactive drugs, the neuronal and psychological idiosyncrasies of drug consumers, and the social environment. Thus, the pharmacological paradigm needs a social-psychological extension, accounting for such effects and more research is needed on how psychoactive drugs operate in a given psychosocial context. Provided growing awareness of these interactions and reciprocal effects, drug-testing procedures probably will have to incorporate social-psychological methods into testing protocols. Furthermore, medical prescription practices probably will have to account for social-psychological factors to maximize drug effectiveness in patients.

Finally, these findings also have legal implications. For example, a perpetrator may blame the physical assault of another person to the influence of acetaminophen and

thus may plead for mitigating circumstances in court. According to my findings, such a court defense may be viable when defendants have committed aggressive or violent crimes while under the influence of acetaminophen. As a consequence, lawyers may use my findings to defend such clients, and courts may have to clarify whether acetaminophen consumption is relevant for determining responsibility for illegal aggressive action under the law.

Conclusion

In summary, my findings suggest that pharmacologically ameliorating the responsiveness to physical pain can also decrease responsiveness to the pain of others. In light of the wide-spread consumption of acetaminophen (Kaufman et al., 2002) and the extensive societal costs of aggressive behavior (Corso et al., 2007), these findings highlight the need for more research on how acetaminophen but also other common physical painkiller, such as nonsteroidal anti-inflammatory drugs or opiates, affect social affect and behavior. Physical analgesics such as acetaminophen are great, because they can help with physical pain, but they are also problematic, because they can suppress reservations to inflict pain on other people.

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Appendix A: Acetaminophen Risk Factors

Participants should not participate in the study, if:

1. They have a history of any liver disorder.
2. They currently taking acetaminophen or a prescription or non-prescription pain suppressant that contains acetaminophen (e.g. Vicodin or oxycodone, also called Percocet or Tylox).
3. They have taken acetaminophen within the last 15 hours.
4. They have an allergic reaction to acetaminophen, the active ingredient in Tylenol.
5. They are currently taking an anticoagulant (e.g. warfarin).
6. They have a history of alcohol abuse or have sought treatment for alcohol abuse.
7. They will drink more than two drinks of alcohol in the 15 hours after completion of the study.
8. They will need to take a drug with acetaminophen or Tylenol in it within the 15 hours after completion of the study.