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Effects of chronic fentanyl administration on physical performance of aged rats

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Abstract

There is growing concern over the increasing use of opioids to treat chronic pain in the elderly primarily because of the potential increased sensitivity to the adverse side effects. Here, we use a preclinical model (male Brown Norway X F344 rats aged 12, 18, 24, and 30 months) to describe the outcome of chronic fentanyl administration (1.0 mg/kg/day) on various physiological and behavioral measures. Continuous fentanyl administration resulted in an initial decrease in food consumption, followed by the development of tolerance to this effect over a 4-week period and a subsequent increase in food consumption during withdrawal. This change in food consumption was associated with decreases in body weight (predominantly due to a loss of fat mass) that was maintained through early withdrawal. After one month of withdrawal, only the 12-month old animals had fully regained body weight. Fentanyl administration resulted in a decrease in grip strength and an increase in locomotor activity that did not differ across age groups. There was no effect of fentanyl administration on rotarod performance. These results demonstrate that while there is a delayed recovery of body mass with age, the observed changes in behavioral responses are uniform across ages.

Keywords

Locomotor activity; Rotarod; Grip strength; Body composition; Osmotic minipump

Introduction

Opioids have been used to treat essentially every type of pain in humans, including acute and chronic pain, for pre-, peri-, and post-surgical situations, for both cancer and non-malignant conditions, and their use is increasing and becoming more widely accepted (Atluri et al., 2003; Bell et al., 2009; Benyamin et al., 2008; Brixner et al. 2006; Garcia del Pozo et al., 2008; Pergolizzi et al., 2008; Trescot et al., 2008). This is especially relevant to the aged

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population where chronic pain due to diffuse conditions (Delgado-Guay & Bruera, 2008; Fine, 2001, 2004; Pergolizzi et al., 2008) such as neuromuscular pain (Helme & Gibson, 2001; Thomas et al., 2004) and arthritis (Donald & Foy, 2004), and to disease-related conditions such as cancer (Potter & Higginson, 2004; Rao & Cohen, 2004) is more prevalent, with estimates of as many as 40% of aged individuals in the community (e.g. > 50 years of age) and 80% in nursing homes (mean age of 75 years) reporting pain that interferes with daily functioning (Fox et al., 1999; Gagliese, 2009; Rustøen et al., 2005; Scudds and Robertson, 2000; Thomas et al., 2004; Zarit et al., 2004). Unfortunately, this pain is often undertreated in aged individuals (Auret & Schug, 2005; Bernabei et al., 1998; Chodosh et al., 2004; Gianni et al., 2009; McNeill et al., 2004). This problem is due in part to the fact that physicians are often reluctant to prescribe opioids to the elderly, given that the full spectrum of adverse side effects (e.g. nausea, constipation, and sedation)(Benyamin et al., 2008; Byas-Smith et al., 2005; Herndon et al., 2002; Swegle & Logemann, 2006) in this particular population is not known (Hutchinson et al. 2007; Lin et al., 2007; Thomason et al., 1998; Wilder-Smith, 2005).

Long-term studies of aging in the human population can be difficult and costly. However, preclinical studies have demonstrated that various behavioral and physiological measures in animals can function as correlates to human measures of declining physical function (Carter et al., 2002; Moser, 2000). These tests evaluate not only basic health metrics such as body weight and composition (fat mass versus muscle mass), but also physical performance measures related to muscle strength, agility, and overall activity. The purpose of the present study was to apply these evaluation tools to study the effects of chronic opioid administration and withdrawal on physical function in rats of various ages. While there are numerous opioids that are used for the treatment of pain, fentanyl is increasingly used for a wide range of conditions including epidural anesthesia, chronic back pain, and cancer pain (Bhambhani et al., 2010; Bell et al., 2009; de Leon-Casasola, 2008; Hong et al., 2010; Manchikanti & Singh, 2008; Pergolizzi et al., 2008; Rauck et al., 2009), and the development of novel formulations and delivery systems such as the transdermal patch makes fentanyl easy to administer chronically in outpatient situations (Grape et al., 2010). In the current study, fentanyl was continuously administered at a dose of 1.0 mg/kg/day for 28 days via osmotic minipumps, as this dosing protocol has previously been shown to produce antinociception (i.e. pain relief) in rats across a wide age range (Morgan et al., 2008; unpublished data). Increased understanding of how age influences the effects of opioids can result in minimizing adverse outcomes, and consequently lead to more effective pain management in the elderly.

Materials and methods

Animals, treatment conditions, and experimental design

Male Fisher 344 x Brown Norway rats, obtained from the National Institute of Aging colony at Harlan Industries (Indianapolis, IN) across four age groups (12, 18, 24, 30 months of age during baseline testing) were used in the present study. This range of ages represents adulthood, middle-age, pre-senescent and senescent portions of the lifespan. Animals were individually-housed in a temperature- and humidity-controlled colony room with a 12-hr light/dark cycle (lights on at 6 AM) with food and water available ad libitum. All surgery and testing was performed during the light cycle. Animals were cared for in accordance with the regulations of the IACUC and with the "Guide for the Care and Use of Laboratory Animals" (ILAR, 1996). In addition, animals were assessed on a weekly basis for signs of overt health problems with measures including, but not limited to, sudden decline in body weight, redness around the eyes and nostrils, ruffled coat, open sores on the tail, and haunched posture.

The experimental timeline is shown in the Table. In brief, upon arrival in the colony, the animals were given 2 weeks to acclimate before baseline testing began for body composition, grip strength, and open field with 2-3 days between each test. Animals within each age group were then randomized to receive osmotic mini-pumps containing either fentanyl (n = 32) or saline (n = 36). After four weeks of drug administration pumps were removed. In the end, 27 fentanyl- and 35 saline-treated animals completed the entire study (12 month: 5 fentanyl, 9 saline; 18 month: 9 fentanyl, 9 saline; 24 month: 7 fentanyl, 9 saline; 30 month 6 fentanyl, 8 saline). Six animals did not complete the experiment presumably due to an adverse interactions between fentanyl and isoflurane. Of primary interest were the behavioral and physiological effects of fentanyl at approximately one week and one month of chronic fentanyl administration. These time points were chosen to be analogous to either short-term treatment regimens related to surgery or outpatient clinical situations, or longer-term disease conditions associated with chronic pain. For ease of description, these time points are referred to as “early” and “late” periods of chronic drug administration or withdrawal. Behavioral tests were conducted on different days, and the order of animal testing was counterbalanced across ages. In general, the duration of the testing was less than 3 hours, and was conducted in the middle of the light/inactive phase.

Surgery and Drug Delivery—Osmotic mini-pumps (Model # 2ML4, Alzet, Durect Corp., Cupertino, CA) containing fentanyl or saline were implanted subcutaneously in the right hindquarter of animals while maintained on isoflurane anesthesia (1.5% at 1.0 L/min O₂). Mini-pumps delivered fluid at a rate of 2.58 µl/hr for 28 days. Fentanyl was delivered at a dose of 1 mg/kg/day. Four weeks after pump implantation, animals were anesthetized and the pumps removed.

Behavioral and Physiological Testing

Food Consumption—Twenty-four hour food consumption data were collected at 7 and 28 days after pump-implantation.

Body Weight and Composition—Body weight was measured weekly for all animals. Determination of body composition was assessed by time domain-nuclear magnetic resonance (TD-NMR) using a Minispec analyzer (Bruker Optics, The Woodlands, TX). TD-NMR testing allows for rapid (approximately 1 min) assessment of body composition in awake, restrained animals. Absolute values for fat, lean, and fluid mass were recorded. At each time point, each animal was tested twice and the average of those results is reported.

Open-field activity—Animals were placed into Plexiglas open-field testing chambers (690 cm × 555 cm) for 5 min and movement was tracked using an overhead camera and computer software (EthoVision, Noldus Information Technology, Wageningen, Netherlands). General activity levels were determined by assessing the total distance traveled. The amount of time spent along the margin of the open field as opposed to the center was taken as a measure of anxiety. The margin was defined as a 3-cm wide strip around the outside of the box.

Grip Strength—Forelimb grip strength was measured using a Chatillon force gauge (Ametek, Largo, FL). Animals were placed so their forepaws were on a wire grid connected to the force gauge. Animals were then pulled away from the wire grid, while the force meter recorded the maximum force exerted on the wire grid. Animals were given three consecutive trials, and the maximum force was taken as a measure of grip strength.

Rotarod—Agility and balance were tested using a Rotamex® rotarod device (Columbus Instruments, Columbus, OH). Animals were given two days of training, in which they were

placed on the 3.5 inch rotarod turning at a rate of 4 rpm. Animals falling in less than 30 s were placed immediately back on the drum for another trial with a maximum of three trials and a time limit of 60 s. Two days after the second training session, baseline performance was assessed. Animals falling prior to 60 s were immediately given a second trial, and trials were a maximum of 300 s in duration.

Statistics—For baseline assessments, one-way ANOVA with age as a factor was used. In cases of unequal variance and non-normal data, a Kruskal-Wallis one way analysis of variance on ranks was performed. For drug administration and withdrawal data, primary statistical analysis consisted of separate two-way repeated measures ANOVA comparing age and treatment phase within each drug group. Subsequent statistical analyses consisted of two-way ANOVA comparing age and drug group for each phase of testing (i.e. early drug, late drug, early withdrawal, and late withdrawal). Student-Newman-Keuls post-hoc tests were performed where appropriate. Differences were considered statistically significant when p -values were less than 0.05. All statistical tests were performed using SigmaStat version 3.11 (Systat Software, Inc, San Jose, CA).

Results

Baseline Characteristics

Age differences in physiology and physical performance prior to drug administration are shown in Figure 1. Food consumption at baseline differed across ages ($H = 18.11$, 3 d.f., $p < 0.001$) with 12-month old animals consuming less than 24- and 30-month old animals. There were also significant age-related differences in body weight ($F_{3, 77} = 27.94$, $p < 0.001$), such that 12-month old animals weighed less and the 24-month old rats weighed more than all other ages. Regarding body composition, 12-month old animals had significantly less fat mass than all other ages ($F_{3, 76} = 5.64$, $p = 0.002$) and significantly more lean mass than 24- and 30-month old animals ($H = 10.87$, 3 d.f., $p = 0.012$). During the initial assessment of physical performance measures, 12-month old animals had greater general activity than all others ($F_{3, 75} = 3.04$, $p = 0.034$), but there were no age differences in time spent in the margin of the activity chamber (a commonly used measure of anxiety), grip strength, or rotarod time.

Food Consumption

Food consumption was altered in fentanyl-treated animals (Figure 2; $F_{4, 93} = 85.01$, $p < 0.001$). During early chronic drug administration, food consumption was significantly decreased relative to baseline, and tolerance appeared to develop to this effect as food consumption returned to baseline levels over the 4 weeks of drug administration. During both early and late withdrawal periods, food consumption was above baseline in all age groups. This change in food consumption was also seen when the fentanyl-treated rats were directly compared to saline-treated rats during early drug and withdrawal, and following four weeks of withdrawal.

Body Weight

Figure 3 shows a significant interaction of age and phase for the fentanyl-treated animals ($F_{12, 102} = 4.14$, $p < 0.001$). Fentanyl administration decreased body weights significantly during early and late drug administration and during early withdrawal, and this effect was greatest in the older animals. During late withdrawal, body weight for 12-month old animals had returned to baseline, but other ages had not fully recovered, with the body weight for 30-month old animals being significantly less than 12-month old animals. Across all phases, direct comparison of fentanyl versus saline treatment revealed lower body weights in fentanyl-treated animals.

Body Composition

Using TD-NMR, decreases in both fat mass and lean mass during drug administration and withdrawal were observed (Figure 4). Similar to body weight, there was an interaction of age and phase for both fat and lean mass in fentanyl-treated animals (fat: $F_{12, 104} = 2.18, p = 0.018$; lean: $F_{12, 104} = 2.50, p = 0.006$). Fentanyl-treated animals lost both fat and lean mass during early and late drug administration as well as during early withdrawal. During late withdrawal, fat and lean mass had returned to baseline levels for 12-month old animals, but older animals were slower to recover, with 30-month old animals showing significantly lower fat and lean mass levels relative to 12-month old animals. During all phases, fentanyl-treated animals had significantly lower levels of fat and lean mass than saline-treated animals. In a direct comparison of tissue type (fat versus lean) and across ages, fentanyl had a greater effect on fat mass than lean mass (all p values < 0.05).

General Activity

In saline-treated animals, there was a habituation-like process with a decrease in activity across phases (Figure 5A; $F_{3, 94} = 23.81, p = <0.001$). In fentanyl-treated animals, only activity during the late withdrawal period was significantly decreased relative to baseline ($F_{3, 81} = 8.88, p = <0.001$). Comparison of fentanyl versus saline showed that saline-treated animals had significantly lower levels of activity during early drug, late drug, and late withdrawal phases. The amount of time spent along the edges of the open field device is often taken as a measure of anxiety. There were little differences in this measure across ages or phases with the exception of a long-lasting increase (i.e. during late withdrawal) in the fentanyl-treated animals (Figure 5B; $F_{1, 54} = 4.46, p = 0.039$).

Grip Strength

During acute drug administration (Figure 6A), age had a significant impact on maximum grip strength similar to previous studies (Carter et al., 2004; Forester & Lal, 1999) with grip strength decreasing with age ($F_{3, 59} = 4.19, p = 0.009$). Fentanyl administration decreased grip strength across ages, but this effect was resolved during late withdrawal (early drug: $F_{1, 59} = 5.28, p = 0.025$; late drug: $F_{1, 56} = 7.907, p = 0.007$).

Rotarod

During all treatment phases (Figure 6B), there was a prominent age effect with older animals having impaired rotarod performance relative to younger animals (early drug: $F_{3, 55} = 5.20, p = 0.003$; late drug: $F_{3, 52} = 9.11, p = <0.001$; late withdrawal: $F_{3, 50} = 7.11, p = <0.001$). However, there was no effect of fentanyl administration on rotarod performance during any phase.

Discussion

There is growing concern over the increasing use of opioids to treat chronic pain in the elderly primarily because of the potential increased sensitivity to the adverse side effects (Benyamin et al., 2008; Hutchinson et al., 2007; Wilder-Smith, 2005). Unfortunately, an increased risk to these effects is not well documented (Bernabei et al., 1998; Fine, 2004; Pergolizzi et al., 2008). The purpose of this study was to assess differential effects of chronic fentanyl administration across ages on various measures of physiology and behavior. Overall, the most profound effects of fentanyl administration were on food consumption, body weight, and body composition. Fentanyl administration resulted in decreases in food consumption and a long-term decrease in body weight, primarily due to decreases in fat mass. Even after a month of withdrawal from fentanyl administration, only the youngest rats had returned to baseline body weight. Given the literature demonstrating

the difficulty of regaining unexpected or unintentional body weight loss and the detrimental functional consequences of such loss in older persons (e.g. Lee et al., 2005; Locher et al., 2007; Miller & Wolfe, 2008; Ritchie et al., 2008), the current findings suggest that body weight should be monitored not only during chronic drug administration but for extended periods following cessation of drug treatment.

Physiological consequences of chronic opioid administration

There is a large literature documenting the effects of opioids on food consumption (e.g. Bodnar, 2004), and in general it is known that acute administration of opioid agonists increases food consumption in rats (Sanger & McCarthy, 1981) while opioid antagonists decrease food consumption (Glass et al., 1999; McLaughlin & Baile, 1983; Yuan et al., 2009). However, studies looking at chronic administration of morphine show decreases in food intake and body weight (Binsack et al., 2006; Levine et al., 1988; Li et al., 2010), while chronic opioid antagonist administration increases food consumption and weight gain (Chen et al., 2004). As hypothesized, chronic fentanyl administration resulted in a decreased food consumption within the first week, and animals became tolerant to this effect as food consumption had returned to baseline after four weeks of fentanyl administration. During withdrawal, fentanyl-treated animals showed an increase in food consumption. Clinically, these data suggest that at the beginning of chronic opioid administration, it is important to make sure that patients are receiving adequate food intake even though these effects are not persistent through the duration of opioid administration or withdrawal.

One predictable consequence of decreases in food consumption is a change in body weight. Of importance is the fact that while obesity leads to major health risks in younger populations, studies have shown that in individuals 60 years old and older, being underweight has a greater risk of mortality and disability than being overweight or even obese (Flegal et al., 2005; Marcell, 2003; Miller & Wolfe, 2008; Paddon-Jones et al., 2008). In the current study, fentanyl administration resulted in a decrease in body weight for all ages throughout the 28 days of drug administration. Using TD-NMR, body composition changes were followed through drug administration and withdrawal, and the overall pattern of decreases in fat and lean (muscle) mass followed a similar course as the changes in body weight. Although food consumption returned to baseline levels by the end of drug administration and increased through one week of withdrawal, body weight (and both fat and lean mass components) remained decreased through withdrawal. Only after one month of withdrawal had these measures started to return to baseline, and the older animals showed less recovery than the younger animals. In general, the effect of fentanyl administration on fat mass relative to lean mass was of a greater magnitude and longer lasting. The fact that only the youngest animals fully regain their body weight at the end of withdrawal even though there are no age differences in food consumption suggests that the decrease in food consumption is not wholly responsible for the decrease in body weight. However, although older individuals may take longer to regain body weight after ending chronic fentanyl administration, lean mass is recovered more quickly than fat mass, which is an important factor in the health of aged individuals (Marcell, 2003).

Behavioral consequences of chronic opioid administration

Given the increasing use of fentanyl, the high prevalence of chronic pain, and the aging of the population, it is critical to identify some of the functional consequences of chronic fentanyl administration across a range of ages. This was especially important as we identified profound changes in body weight and composition that were longer-lasting in the oldest animals and could lead to decreased strength and functional independence, and eventually increased frailty, disability, and mortality.

Similar to previous studies, there were age-related differences in overall activity levels assessed in an open field at baseline, and during the initial drug administration phase declines were observed in rotarod and grip strength (Carter et al., 2004; Forster & Lal, 1999). Fentanyl appeared to have effects on both activity levels (increases) and grip strength (decreases) at the late drug time point, and these effects were not maintained into the late withdrawal phase. These findings are consistent with the literature showing that repeated administration of mu opioid agonists (including fentanyl and morphine) can result in long-lasting increases in locomotor activity levels in rats (e.g. Khallouk-Bousselmame & Costentin, 1994; Powell & Holtzman, 2001; Rauhala et al., 1995; Trujillo et al., 2004). Clinically, extended fentanyl administration increases activity, although it is unclear if this is a direct effect of fentanyl or a by-product of mitigation of chronic pain in these patients (Agarwal et al., 2007). Age-related decreases in rotarod performance were maintained throughout all phases of drug/saline administration, however fentanyl did not influence performance. These findings suggest that while chronic fentanyl administration has lasting effects on physiological measures, this does not necessarily translate into decrements observed in these behavioral measures. Importantly, these data provide information suggesting that strong opioids such as fentanyl do not necessarily result in more dramatic and potentially dangerous adverse behavioral side effects with increases in age.

Implications

The relative age of the population is increasing, there is a high prevalence of age-related chronic pain in this population, and opioids are being used more commonly for a greater number of clinical conditions. The potential adverse physiological and behavioral outcomes of chronic opioid administration in aged populations are relatively unknown. The present study characterized some differential consequences of chronic fentanyl administration to rats of various ages. Chronic opioid administration had effects on both physiological measures (body weight, body composition, food consumption) and behavioral tests (grip strength and open field). Lasting effects were only observed in these physiological measures. Fentanyl administration decreased body weight (both fat mass and lean, muscle mass) across all ages, but older animals took longer to recover body weight following cessation of fentanyl administration. This slow recovery in body weight occurs even in the face of apparent tolerance to the anorectic effects as food consumption levels returned to then surpassed baseline levels of intake. On the positive side, these dramatic changes in body weight and consumption did not necessarily translate into long-lasting functional deficits assessed using a number of behavioral measures. Taken together, these data suggest that chronic opioid administration to aged individuals can have dramatic and long-lasting effects that should be routinely assessed even following prolonged periods of withdrawal from the drug.

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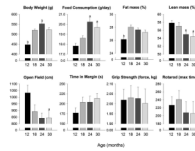


Figure 1. Baseline measures

Assessments made before implantation of osmotic pumps across the four age groups. Data are presented as means \pm SEM. ^a $p < 0.05$ compared with 12 month old animals, ^b $p < 0.05$ compared with all other ages.

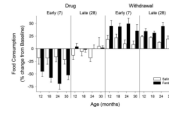


Figure 2. Food consumption

Changes in food consumption during fentanyl/saline administration (“Drug”) and “Withdrawal”. Each phase is divided into an “Early” and “Late” stage, and the number in parentheses represents the number of days following the minipump implantation or removal that the measure was taken. Data are presented as percent change from baseline (mean \pm SEM) for each age group. Note that fentanyl decreased food consumption across ages during early assessments, and increased food consumption throughout withdrawal.

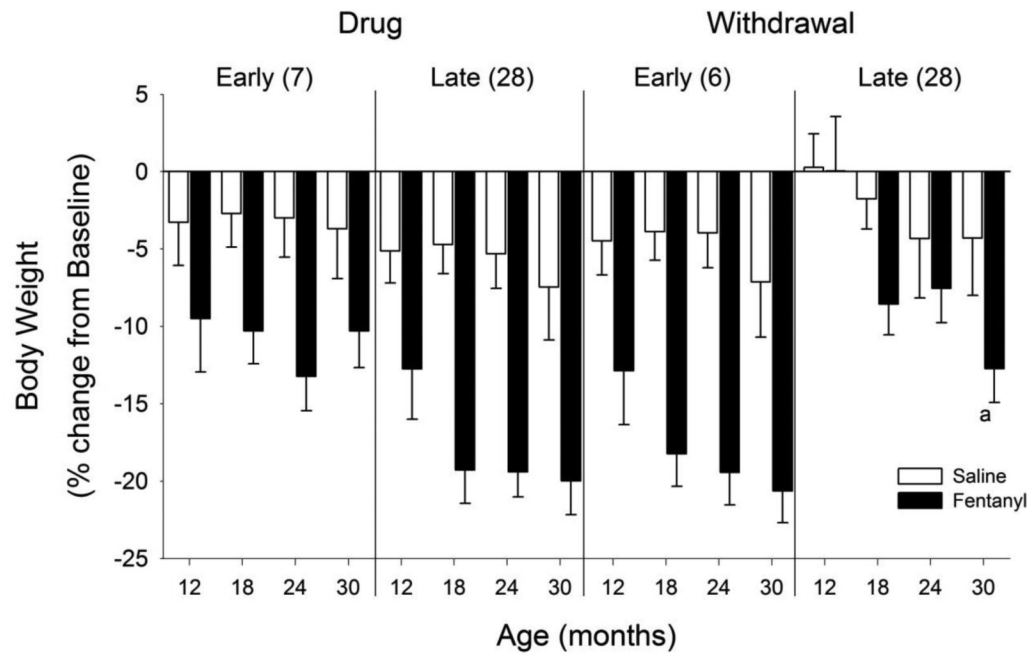


Figure 3. Body weight

Changes in body weight during fentanyl/saline administration and withdrawal. Other details as in Figure 2. Note that fentanyl resulted in decreased body weight across ages during the Early and Late drug administration, and during Early withdrawal. By 28 days of withdrawal, the youngest animals returned to baseline levels. ^a $p < 0.05$ compared with 12 month old animals.

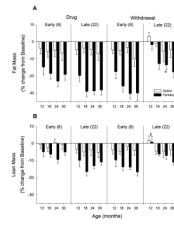


Figure 4. Body composition

Changes in (A) fat mass and (B) lean/muscle mass during fentanyl/saline administration and withdrawal. Other details as in Figure 2. Note that fentanyl resulted in decreased fat and muscle mass across ages during Early and Late drug administration, and during Early withdrawal. By 22 days of withdrawal, the youngest animals returned to baseline levels. ^a $p < 0.05$ compared with 12 month old animals, ^b $p < 0.05$ compared with all other ages.

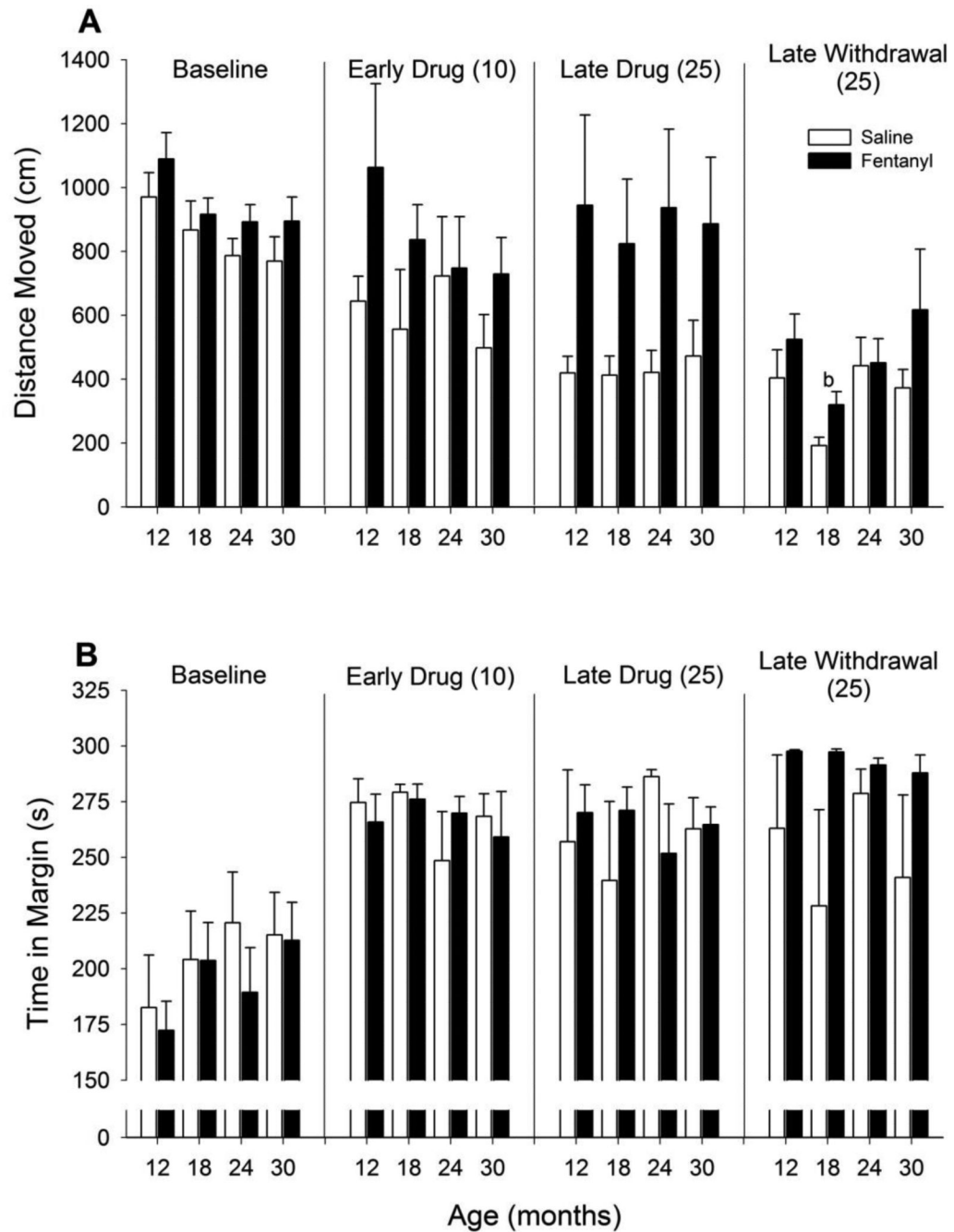


Figure 5. Open field activity

Changes in (A) total distance traveled and (B) time spent in the margin. Other details as in Figure 2. Note that saline-treated animals showed decreased activity over repeated testing (i.e. habituation), whereas fentanyl resulted in heightened levels of activity throughout drug administration. Following 24 days of drug withdrawal, fentanyl-treated animals spend essentially the entire session in the margin, a finding consistent with increased levels of anxiety. ^b $p < 0.05$ compared with all other ages.

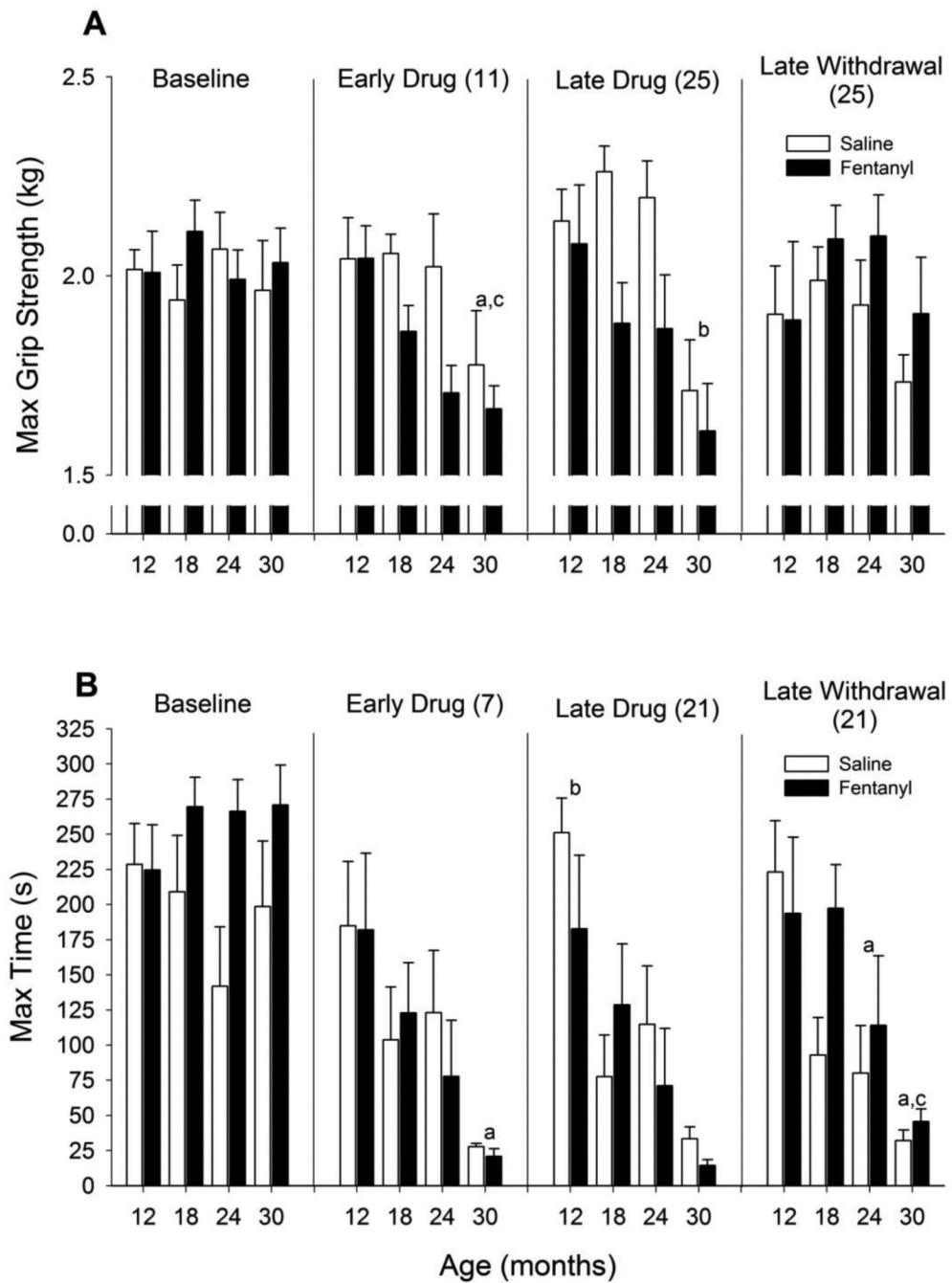


Figure 6. Physical performance measures

Changes in (A) maximum grip strength and (B) time spent on rotarod. Other details as in Figure 2. Note decreases in grip strength during fentanyl administration although this decrease does not persist after 25 days of withdrawal. ^a $p < 0.05$ compared with 12-month old animals, ^b $p < 0.05$ compared with all other ages, ^c $p < 0.05$ compared with 18-month old animals. For rotarod performance, there were decreases in time with increasing age regardless of drug treatment. ^a $p < 0.05$ compared with 12-month old animals, ^b $p < 0.05$ compared with all other ages, ^c $p < 0.05$ compared with 18-month old animals.

Table 1

Timeline of experimental events

Phase	Day	Experimental event
Baseline	0	Arrival in lab
	14-42	Open field, grip strength, TD-NMR, Rotorod, food consumption, and body weight measures
Drug / saline administration	0	Implant pump
	7	Body weight, food consumption, Rotorod
	8	TD-NMR
	10	Open field, grip strength, TD-NMR, Rotorod, food consumption, and body weight measures
	11	Grip strength
	21	Rotarod
	22	TD-NMR
	24	Open field
	25	Grip strength
	28	Food consumption, body weight
Withdrawal	0	Remove pump
	6	Body weight
	7	Food consumption, TD-NMR
	21	Rotarod
	22	TD-NMR
	24	Open field
	25	Grip strength
	28	Food consumption, body weight