

AQUATIC POLLUTION

Pharmaceutical pollution influences river-to-sea migration in Atlantic salmon (*Salmo salar*)

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Despite the growing threat of pharmaceutical pollution, we lack an understanding of whether and how such pollutants influence animal behavior in the wild. Using laboratory- and field-based experiments across multiple years in Atlantic salmon (*Salmo salar*; $n = 730$), we show that the globally detected anxiolytic pollutant clobazam accumulates in the brain of exposed fish and influences river-to-sea migration success. Clobazam exposure increased the speed with which fish passed through two hydropower dams along their migration route, resulting in more clobazam-exposed fish reaching the sea compared with controls. We argue that such effects may arise from altered shoaling behavior in fish exposed to clobazam. Drug-induced behavioral changes are expected to have wide-ranging consequences for the ecology and evolution of wild populations.

Pharmaceutical pollution poses a serious threat to biodiversity, ecosystem services, and public health (1, 2). Many pharmaceuticals enter aquatic ecosystems during drug manufacture, use, and disposal (3). Indeed, almost 1000 different active pharmaceutical substances (or their transformation products) have now been detected in waterways across the globe (3, 4). These contaminants often target evolutionarily conserved neurobiological pathways, are designed to be effective at low concentrations, and can persist in the environment because of their continuous release and/or resistance to degradation (3, 5).

Although research has shown that high concentrations of pharmaceutical pollutants can have lethal consequences for wildlife (6, 7), recent work has demonstrated that even the dilute pharmaceutical concentrations that are routinely detected in the environment can have extensive sublethal effects on species' behavior (5, 8–10). This is especially true of

behavior-modifying psychoactive pharmaceuticals (e.g., anxiolytics and antidepressants). These pollutants have been repeatedly detected in the tissues of wild aquatic organisms—including in the brain (11, 12)—at concentrations known to act on neural pathways that mediate key behaviors (13, 14).

Much of the existing research on the behavioral effects of pharmaceutical pollutants has investigated impacts under simplified conditions in the laboratory that fail to capture real-world complexity, assuming that drug-induced changes likely affect organismal performance in the wild (5, 9). Although this research provides crucial baseline data on both the types and concentrations of pharmaceuticals that can modify animal behavior, we lack an understanding of whether these changes also occur in the wild and whether they have actual consequences for organismal performance and survival. Moreover, although many laboratory studies expose organisms to a single contaminant in isolation (9), organisms in the wild are typically exposed to multiple pharmaceuticals concurrently. This often includes exposure to combinations of pharmaceuticals that are known to produce adverse effects in humans as a result of chemical interactions (e.g., opioid analgesics and anxiolytics), resulting in potential synergistic and additive effects.

Here, we conducted a controlled laboratory study in conjunction with a large field-based experiment across 2 separate years to investigate how psychoactive pharmaceutical pollutants—when experienced in isolation and as a mixture—influence behavior and river-to-sea migration in Atlantic salmon (*Salmo salar*). Atlantic salmon (hereafter referred to as “salmon”) are a mostly anadromous fish native to Europe and North America that begin their life in freshwater rivers and streams (15, 16). After 1 to 4 years in fresh water, juvenile salmon in our study population undergo a complex physiological and

morphological transformation from parr to smolts (i.e., young salmon during their initial migration phase) before undertaking a seaward migration in the spring (15). At sea, salmon feed and grow for 1 to 4 years before reaching sexual maturity and returning as adults to reproduce in their natal rivers (15). Seaward migration, therefore, represents a crucial life-history event for juvenile salmonids, which may be vulnerable to disruption by exposure to psychoactive pharmaceuticals in rivers and streams (17). Indeed, salmon populations have suffered substantial declines in recent years owing to anthropogenic environmental change, with chemical pollution being identified as a contributing factor (18–20). Given that salmon are a species of substantial cultural and commercial importance whose conservation is listed as high priority in Europe and North America (18), understanding how psychoactive pharmaceutical pollutants influence migration success in this species is vital for conservation and management efforts.

Recent research has shown that exposure to environmentally realistic concentrations of benzodiazepine pharmaceuticals (a common class of psychoactive drugs prescribed for anxiety disorders) can affect fish behavior in the laboratory (8, 21), including in salmonids (22). Previous work has also shown that benzodiazepine pollutants can influence migration in salmonid fishes when released into the wild (23–26). However, these studies have predominantly investigated migration over short distances (e.g., ~100 m) or exposed fish to high drug concentrations (e.g., 200 $\mu\text{g liter}^{-1}$) that exceed detected environmental levels. Consequently, it remains unknown whether exposure to environmentally relevant psychoactive drug concentrations—either alone or in mixtures—affects the migration success of salmon.

We exposed 279 salmon smolts to one of four pharmaceutical treatments (control, clobazam, tramadol, or clobazam-tramadol mixture) in the wild using previously validated slow-release chemical implants (27, 28). We ensured that there was no statistical difference in smolt body mass between treatment groups before release. The downstream migration of exposed smolts was tracked with acoustic telemetry tags that were detected on receivers placed across a ~28-km stretch of the River Dal in central Sweden (Fig. 1). This section of the river first flows into a large reservoir (Storfjärden; area of ~18.7 km^2), after which it passes through a series of rapids and two hydropower dams before eventually discharging into the Baltic Sea. Experiments were replicated across two years (2020 and 2021) to reduce the potential impact of natural yearly variation in migration conditions.

Before undertaking their downstream seaward migration, smolts were implanted with either a control implant (no pharmaceuticals),

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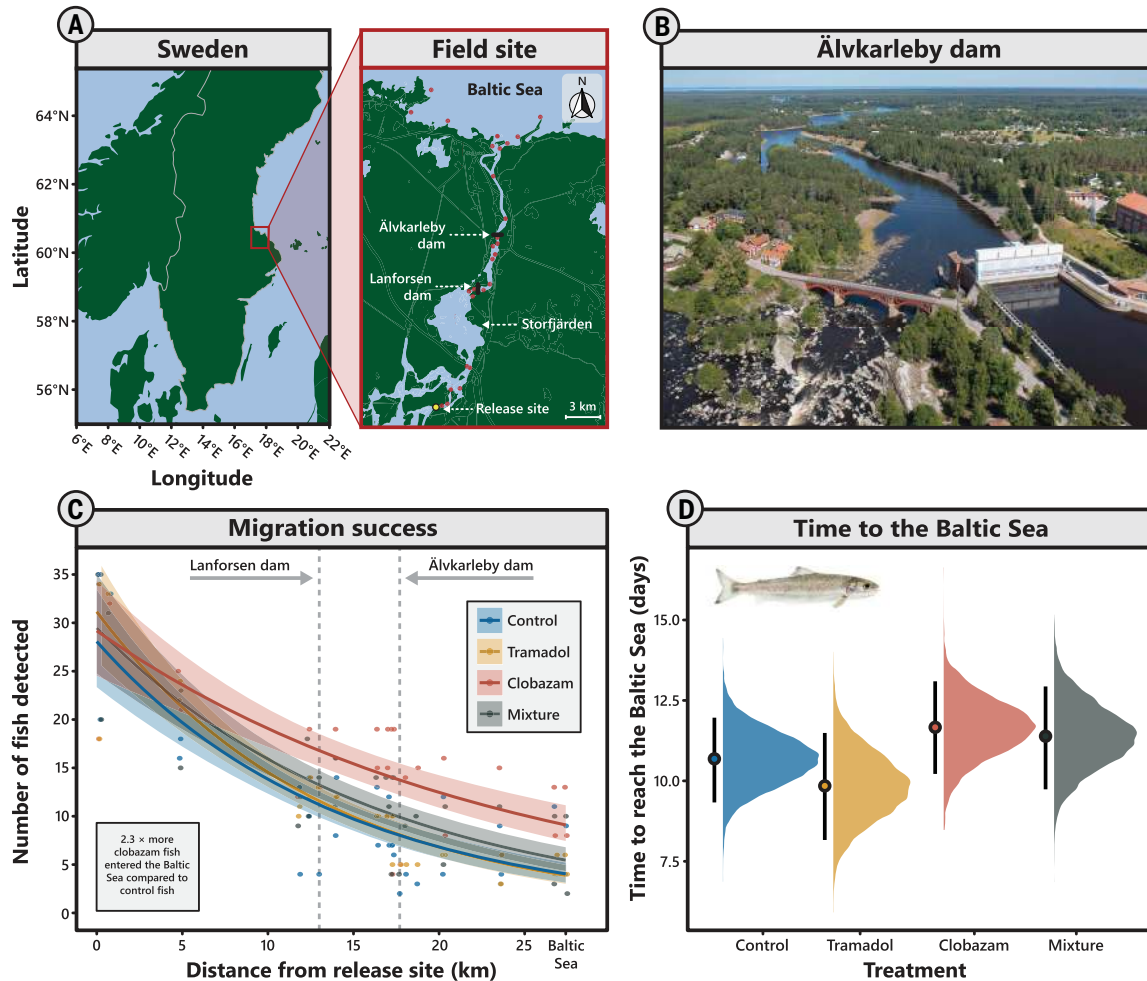


Fig. 1. Clobazam influenced Atlantic salmon migration. (A) Simplified illustration of the field site, showing the locations of the release site (yellow circle) and acoustic receivers (red circles) across 2020 and 2021. Select receivers at areas of high receiver density are not shown to aid visualization. Similarly, dam size has been enlarged to enable visualization (see table S3 for precise receiver locations). (B) Aerial image of Älvkarleby dam (one of the two dams within our field site), with the River Dal flowing toward the Baltic Sea in the background [credit: Getty Images/Marcus Lindstrom]. (C) The number of fish detected for each treatment group as a function of distance (km) from the release site. Trend lines display conditional effects of distance from the

release site extracted from the Bayesian generalized linear model, with colored ribbons denoting 89% highest density intervals (HDI). Vertical dashed lines show the approximate locations of the Lanforsen and Älvkarleby dams. (D) Number of days taken for fish that successfully migrated to reach the Baltic Sea. Estimates represent median marginal effects, with error bars denoting 89% HDI of the posterior distribution (colored distributions) of each treatment group extracted from the Bayesian linear mixed-effects model. Results from both plots are averaged over the effect of year and are representative of an average-sized fish [Atlantic salmon smolt photo insert credit: Jörgen Wiklund].

the benzodiazepine anxiolytic clobazam ($50 \mu\text{g g}^{-1}$ clobazam implant), the opioid analgesic tramadol ($50 \mu\text{g g}^{-1}$ tramadol implant), or a single implant containing a drug mixture ($50 \mu\text{g g}^{-1}$ of clobazam and $50 \mu\text{g g}^{-1}$ of tramadol). Notably, clobazam and other benzodiazepine drugs with the same mechanism of action are commonly detected in wastewater-affected aquatic ecosystems around the world, including within the native distribution of salmon and other anadromous fishes (3, 29, 30). This is also true of tramadol and other opioid drugs (30–32). What is more, prescription and consumption of benzodiazepines has increased over the last several decades (33, 34). Although global opioid use decreased from 2009 to 2019,

consumption rates increased in high-income countries across the same time period (35), highlighting the ongoing threat of psychoactive pharmaceutical pollution. Clobazam and tramadol have well-documented adverse chemical interactions when prescribed together to human patients (36) and thus could be predicted to negatively affect wildlife when exposed concurrently. A simultaneous laboratory-based study was performed on 256 salmon smolts to validate our chemical implant methods and confirm that pharmaceuticals from the implants were present in fish tissues, including the brain (28) (fig. S1 and tables S4 to S6). These tissue concentrations are approximately reflective of benzodiazepine and opioid drug con-

centrations reported in wild fish (37–39) and fish exposed to environmentally realistic benzodiazepine waterborne concentrations in the laboratory (21), allowing us to gain insights into how these drugs may be influencing wild fish in real-world settings. Furthermore, broad-spectrum chemical analysis of water samples collected in the River Dal found low background concentrations of tramadol [$2.11 (\pm 0.29) \text{ ng liter}^{-1}$ in 2020 and $1.57 (\pm 0.07) \text{ ng liter}^{-1}$ in 2021] but no evidence of clobazam contamination (table S1). Critically, neither clobazam nor tramadol were detected in any tissue from control treatment fish from the laboratory exposure experiment that had been housed in fresh water supplied from the River Dal,

ensuring that our control treatment fish in the field study were free from clobazam and tramadol contamination. This controlled, field-based experimental approach ensures that any differences between our treatment groups in behavior and migration can be attributed to the effects of the clobazam and/or tramadol implants.

Clobazam influenced river-to-sea migration

Clobazam exposure increased the number of salmon smolts that reached the Baltic Sea across 2020 and 2021 (Fig. 1C and table S9). Specifically, there was an interaction between treatment and distance from the release site on the number of smolts detected at receivers along the river, with a greater number of clobazam-exposed fish being detected downstream relative to all other treatment groups (table S9). This resulted in more clobazam-exposed smolts ultimately entering the Baltic Sea each year {estimate [89% highest density interval (HDI)] = 8.98 fish [7.59, 10.50]}, relative to the control [3.99 fish (3.18, 4.83)], tramadol [3.83 fish (3.07, 4.60)], or mixture [5.39 fish (4.43, 6.41)] treatment groups (table S10). The average predicted proportion of smolts lost during their seaward migration ranged from 74.3% in the clobazam-exposed group to 84.6, 88.6, and 88.9% in the mixture, control, and tramadol treatment groups, respectively. In contrast to predictions, more smolts from the mixture-exposed group ultimately reached the Baltic Sea as compared with the control and tramadol groups (tables S9 and S10). Furthermore, in 2021, one control, one mixture, two tramadol, and four clobazam-exposed smolts were detected by receivers located in the Baltic Sea, demonstrating that at least a portion of the smolts survived their journey out into the sea. These numbers are likely underestimates because the receivers deployed in the sea were unable to fully cover the very large area (i.e., tagged smolts could pass through the Baltic Sea without being detected on the receiver array in 2021; there

were no Baltic Sea receivers in 2020 because of logistical constraints).

The higher numbers of clobazam-exposed smolts reaching the sea were likely not due to differences in overall migration speed across 2020 and 2021 (Fig. 1D and table S11). Indeed, we found no substantial difference in the number of days taken to ultimately reach the Baltic Sea among smolts that successfully migrated in the control [10.69 days (9.33, 11.96)], clobazam [11.66 days (10.22, 13.09)], and mixture [11.39 days (9.74, 12.93)] treatment groups. However, there was a negligible difference in migration speed between the clobazam and tramadol treatment groups, with tramadol-exposed smolts migrating marginally faster [9.84 days (8.16, 11.49)]; table S11). We found no difference in migration speed between tramadol-exposed smolts and smolts from either the control or mixture treatment groups (table S11). Regardless of treatment, smolts took marginally less time to reach the Baltic Sea (migrated faster) in 2021 compared with 2020 [estimate (89% HDI) = -1.25 (-2.64, 0.13)]. There were minimal differences between 2020 and 2021 in water temperature in the lower River Dal (fig. S2), suggesting that the faster migration speeds observed in 2021 were most likely due to increased daily water flow in the river (fig. S3). Moreover, upstream movements (see supplementary materials) were equally rare among all treatment groups (table S12), suggesting that fish that were not detected on downstream receivers had most likely died rather than simply returning upstream. It is also possible that, after initiating migration, smolts may have stopped and remained in a certain section of the river until after the acoustic receivers had been collected, before eventually continuing their migration. This may be particularly true for lower portions of the river and the estuary. Indeed, some salmon smolts are known to delay their sea entry and increase their estuary residence time based on individual physiological traits (40). However, estuary environments

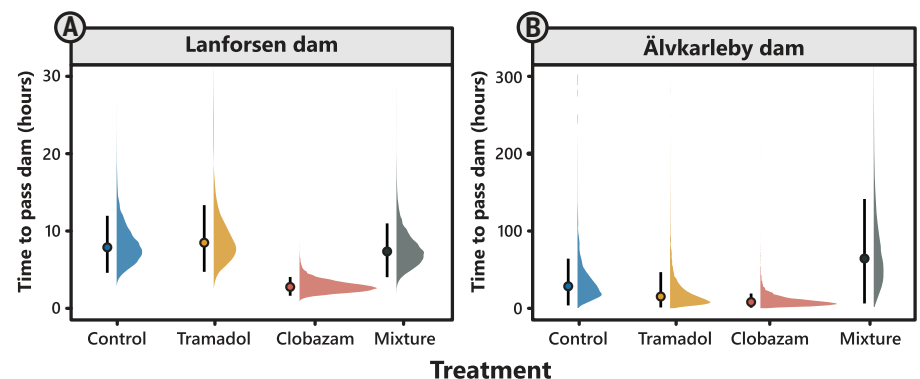
are often associated with dramatic increases in mortality risk (up to 36% per km) for smolts (41), further suggesting that those smolts that did not make it to the Baltic Sea had likely died prior to sea entry.

Clobazam influenced dam-passage speed

Hydropower dams represent a widespread barrier impeding the downstream seaward migration of salmon smolts (41). Prior research has demonstrated that smolts can suffer high mortality as a direct result of injury when passing dams (41). In addition, delayed migration due to hydropower dams has also been associated with higher predation threat, increased energy expenditure, and mistimed sea entry in salmon smolts (41–43), suggesting that the ability to successfully navigate dam barriers is a critical determinant of migration success. Crucially, more than 1 million barriers fragment European rivers, including 7628 dams in Sweden alone (44). Many of these same rivers are known to be contaminated with benzodiazepine and opioid analgesic pollutants (3, 45), emphasizing the potential for both human-made barriers and pharmaceutical pollution to influence migration dynamics in salmon.

To further understand the increased number of clobazam-exposed smolts reaching the sea, we investigated whether and how pharmaceutical exposure may have influenced their ability to pass through the turbines at two hydropower dams along the River Dal. Clobazam exposure decreased the time taken to pass through the turbines of both the Lanforsen (four Kaplan turbines) and Älvkarleby (five Francis turbines and one Kaplan turbine) dams across 2020 and 2021 (Fig. 2 and tables S14 and S16). On average, clobazam-exposed smolts took 2.77 (1.63, 4.06) hours to pass the Lanforsen dam, which was 2.5 to 3 times faster than smolts from the control [7.89 hours (4.59, 11.96)], tramadol [8.49 hours (4.72, 13.35)], and mixture [7.36 hours (4.03, 10.98)] treatment groups (table S14). Smolts were also faster at passing

Fig. 2. Clobazam influenced dam-passage speed. The time taken for fish to pass both the (A) Lanforsen (2020 and 2021) and (B) Älvkarleby (2020 only) dams. Estimates represent median marginal effects, with error bars denoting 89% highest density intervals (HDI) of the posterior distribution (colored distributions) of each treatment group extracted from the Bayesian generalized linear mixed-effects model. Data for Älvkarleby are from 2020 only owing to the absence of a direct downstream receiver in 2021. The tails of the distributions from both plots exceed the displayed maxima of the figures. However, we restricted the Cartesian coordinates of the plots so that comparisons between group medians could be better visualized. Results from (A) are averaged over the effect of year, and results from both plots are representative of an average-sized fish.



the Lanforsen dam in 2021 when compared with 2020, regardless of treatment [estimate = -1.12 (-1.65, -0.53)]. However, despite differences in dam-passage speed, there were no differences between the treatment groups in the predicted probability of successfully passing the Lanforsen dam (median predicted probability >95% for all treatment groups; table S13).

Clobazam-exposed smolts also passed the Älvkarleby dam faster, taking an average of 8.14 (0.82, 19.18) hours to pass the dam, which was 2 to 8 times faster than smolts from the control [28.52 hours (3.78, 64.23)], tramadol [15.29 hours (1.14, 46.82)], or mixture [64.44 hours (4.84, 139.77)] treatment groups in 2020 (table S16; data for Älvkarleby are from 2020 only owing to the absence of a direct downstream receiver in 2021). Similarly to the results with the Lanforsen dam and notably, there was little evidence for any considerable differences among treatments in the predicted probability of successfully passing the Älvkarleby dam (table S15). Thus, although we found evidence that clobazam-exposed smolts moved across the dams more rapidly, this did not translate into any substantial differences in dam-crossing success in exposed fish.

Clobazam altered the shoaling behavior of smolts under controlled laboratory conditions

The results of our field-based experimental study show that clobazam exposure increased both the number of fish reaching the sea and dam-passage speed in salmon. Previous research has shown that benzodiazepine pollutants can alter social behavior in fish (8, 46) and has highlighted that shoaling behavior may be an important component of salmon smolt migration (47, 48). Thus, to further investigate the findings from our multiyear field study, we performed an additional laboratory study in 2022 to investigate whether the differences we saw were related to changes in shoaling behavior. Two-year-old (the same age as those used in the field experiment) salmon smolts ($n = 126$) were randomly allocated to one of three pharmaceutical exposure groups: control ($0 \mu\text{g g}^{-1}$; implant without clobazam; $n = 42$), low ($50 \mu\text{g g}^{-1}$ of clobazam implant; the same concentration as that used in the field-based migration experiment; $n = 42$), or high ($150 \mu\text{g g}^{-1}$ of clobazam implant; a concentration higher than environmentally detected levels, acting as a positive control; $n = 42$). Smolts from each exposure treatment were randomly allocated to one of seven assay groups (seven groups per exposure treatment; six smolts from the same exposure treatment within each group). We filmed the shoaling behavior of these fish in large arenas from above and repeatedly measured the group convex hull area (hereafter “group area”) and the median nearest-neighbor

distance of shoals—two measures of group cohesion in which smaller values represent more-cohesive groups (49, 50). Predator avoidance is one suggested benefit of shoaling behavior, with fish being known to form more-cohesive groups when exposed to high levels of predation (51, 52). Thus, we conducted behavioral trials in both the absence (three trials per group) and presence (three trials per group) of a common smolt predator (the northern pike, *Esox lucius*) to determine whether any effects of clobazam on shoaling were dependent on predator context. Using a separate cohort of 69 salmon smolts, we confirmed that tissue concentrations of clobazam from the low-treatment group were similar to those detected in clobazam-exposed smolts in the field experiment (fig. S4 and tables S7 and S8).

We found that exposure to both low and high concentrations of clobazam altered the shoaling behavior of smolts (Table 1; detailed description of results provided in supplementary materials). Clobazam-exposed groups displayed a larger group area and median nearest-neighbor distance than control groups in the presence of a predator (Fig. 3, Table 1, and tables S17 and S18). However, there were minimal differences between treatment groups in the absence of a predator (Fig. 3B, Table 1, and table S17). Why clobazam-exposed groups differed from unexposed conspecifics only in their shoaling behavior in the presence of a predator is not entirely clear, but we argue that clobazam could have altered the risk-taking behavior of exposed smolts. Indeed, clobazam-exposed treatment groups were more responsive to varying predator conditions, with both low- and high-exposure groups demonstrating a substantially larger change in both group area and median nearest-neighbor distance across predator conditions when compared with controls (Fig. 3, Table 1, and tables S17 and S18). Given that previous work has reported associations between shoal cohesion and predation risk (51–53), our results suggest that clobazam exposure may have increased risk-taking behavior and sub-

sequently decreased shoal cohesion in exposed smolts.

Conclusions

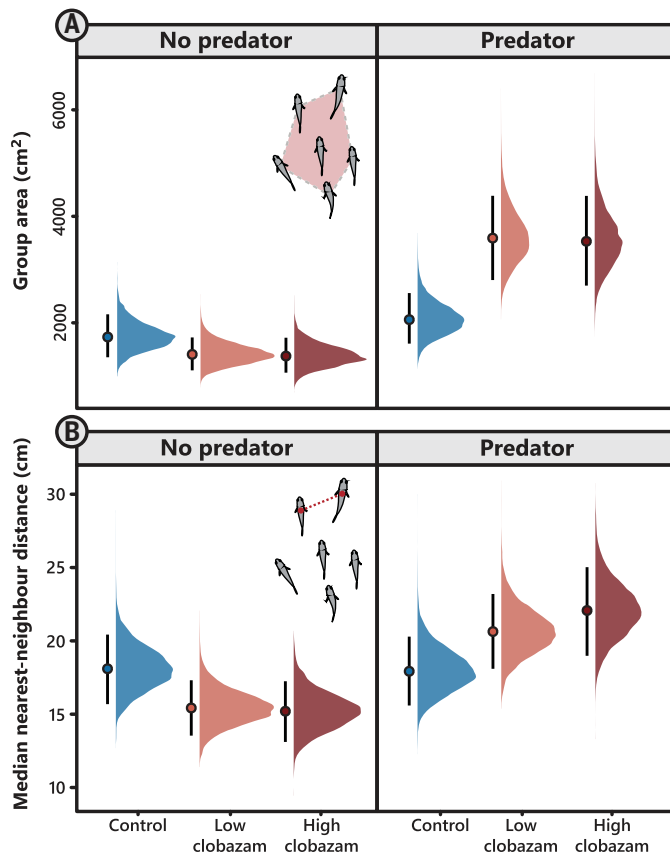
We have demonstrated that experimental exposure to pharmaceutical pollution at environmentally relevant levels alters the behavior and subsequent river-to-sea migration of Atlantic salmon. Specifically, clobazam exposure resulted in a greater number of smolts ultimately moving through the River Dal and entering the Baltic Sea, relative to controls. However, there was no evidence for substantial treatment differences in the probability of successfully passing the two hydropower dams along the River Dal, suggesting that the increased number of clobazam-exposed smolts was likely not due to increased survival when passing through the dams. Moreover, although clobazam-exposed smolts moved more quickly across the dams when compared with all other treatment groups, there was no evidence for substantial treatment differences in overall migration speed for those that completed their migration to the sea.

Complementary laboratory assays showed that clobazam exposure altered the shoaling behavior of salmon smolts, a trait thought to be important for their migration (41, 47, 48). Specifically, clobazam-exposed salmon shoals were less cohesive in the presence of a predator compared with controls. Previous research has shown that fish often form more-cohesive groups when exposed to high levels of predation (51, 52) and that fish in larger groups have a lower predation risk (53). Similarly, prior work suggests that the shoaling behavior of migrating salmon smolts may be an antipredator strategy (41). Together, these results suggest that clobazam exposure may have altered risk-taking behavior in salmon smolts, a finding that is consistent with previous work on fish exposed to other benzodiazepine drugs (21, 54, 55). Therefore, the heightened risk-taking behavior and decreased cohesion of clobazam-exposed smolt shoals when under predation threat would be predicted to make them more vulnerable to

Table 1. Estimated marginal means [89% highest density interval (HDI)] of group convex hull area (group area) and median nearest-neighbor distance of salmon smolt shoals from the control ($0 \mu\text{g g}^{-1}$ of clobazam implant), low-clobazam ($50 \mu\text{g g}^{-1}$ of clobazam implant), and high-clobazam ($150 \mu\text{g g}^{-1}$ of clobazam implant) treatment groups during the laboratory shoaling assay. Lower values indicate greater cohesion.

	Group area (cm^2) Marginal mean (89% HDI)		Median nearest-neighbor distance (cm) Marginal mean (89% HDI)	
	No predator	Predator	No predator	Predator
Control	1733 (1357, 2163)	2060 (1609, 2557)	18.10 (15.69, 20.43)	17.93 (15.59, 20.28)
Low clobazam	1407 (1107, 1725)	3591 (2793, 4370)	15.42 (13.54, 17.31)	20.63 (18.10, 23.20)
High clobazam	1375 (1064, 1720)	3531 (2699, 4384)	15.20 (13.11, 17.25)	22.07 (18.85, 24.89)

Fig. 3. Clobazam altered the shoaling behavior of Atlantic salmon smolts. The (A) convex hull group area (cm²) and the (B) median nearest-neighbor distance (cm) of shoals exposed (or not; i.e., control group) to low (50 µg g⁻¹ clobazam implant) or high (150 µg g⁻¹ clobazam implant) concentrations of clobazam. Assays were performed in both the presence and absence of a fish predator (the northern pike, *Esox lucius*). Estimates represent median marginal effects, with error bars denoting 89% highest density intervals (HDI) of the posterior distribution (colored distributions) of each treatment group extracted from the Bayesian generalized linear mixed-effects model.



predation in the wild (where predators are abundant), resulting in reduced migration success.

However, our study found that more clobazam-exposed smolts ultimately reached the Baltic Sea relative to controls. We surmise that heightened risk-taking behavior and decreases in group cohesion, as a result of clobazam exposure, could have facilitated passage through the hydropower dams along the River Dal, resulting in the faster dam passage speeds and higher numbers of successful migrants observed. Hydropower dams represent a major barrier to migrating salmon smolts. Indeed, dam passage has been associated with injury and increased energy expenditure in salmon (41–43). Similarly, dam impoundments have been found to result in an almost fivefold increase in predation risk relative to free-flowing river sections in salmon smolts (56), suggesting that dam passage is a high-risk event for salmon and is a critical determinant of migration success. Although collective navigation has been shown to facilitate passage through human-made barriers in upstream-migrating adult Pacific salmonids (*Oncorhynchus* sp.) (57, 58), previous research has found that solitary fish navigated past downstream barriers up to 23 times faster than fish in social groups (59). In addition, benzodiazepine pollutants have been shown to decrease cortisol expression (22) and the stress response (55) of exposed fish, potentially suggesting that stress experienced during dam

passage may have been reduced in clobazam-exposed smolts. Taken together, our results suggest that clobazam-exposed smolts may have adopted a more risk-prone and solitary strategy than unexposed conspecifics when undertaking their seaward migration.

We emphasize that any changes to migration dynamics are expected to have long-term consequences for the viability of contaminated populations. The extent of these impacts is difficult to predict, especially when considering realistic exposure scenarios in which entire ecosystems, comprising multiple trophic levels, are exposed. Nevertheless, our results demonstrate the capacity for pharmaceutical pollution to influence key fitness-related behaviors of animals in the wild, with potentially wide-ranging consequences.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

Figs. S1 to S4

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MDAR Reproducibility Checklist

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