Table 2. Therapies Targeting the Underlying Cause of Fragile X Syndrome (FXS) That Are Undergoing Clinical Trials

Agent	Clinical Evidence in FXS	Status of Planned or Ongoing Trials
mGluR5 Antagonists		
AFQ056/ mavoglurant	Phase 2, randomized, double-blind, placebo-controlled study[131] 30 males aged 18–35 years with FXS Significant difference between AFQ056/mavoglurant and placebo for RBS-R overall but not ABC-C (primary outcome) or other secondary outcomes Subgroup analysis of individuals with fully methylated *FMR1* promoter showed significant differences between AFQ056/ mavoglurant and placebo for ABC, CGI-Improvement, CGI efficacy, RBS-R, SRS, VAS, but not VABS, as well as measures of hyperactivity, inappropriate speech, and stereotypic behavior	Ongoing: 2 phase 2b, double-blind, randomized, placebo-controlled trials in individuals with FXS to assess the efficacy of 3 AFQ056/ mavoglurant doses on behavioral symptoms One in adolescents (12–17 years; NCT01433354) One in adults (18–45 years; NCT01348087)
STX107	None	Planned: phase 2, randomized, double-blind, placebo-controlled study of a single dose of STX107 (10 mg or 30 mg) in 16 adults with FXS (ClinicalTrials.gov identifier: NCT01325740) Recruitment suspended pending further evaluation
RO4917523 (RG7090)	Phase 2 trial in 40 individuals with FXS reported favorable safety profile for RG7090 (ClinicalTrials.gov identifier: NCT01015430)	Recruiting: phase 2, randomized, double-blind, placebo-controlled efficacy and safety study of 180 individuals with FXS aged 16–50 years (ClinicalTrials.gov identifier: NCT01517698) Individuals will be treated with RG7090 0.5 mg or 1.5 mg over 12 weeks Recruiting: phase 2, randomized, double-blind, placebo-controlled safety and preliminary efficacy study of 45 individuals with FXS aged 5–13 years (ClinicalTrials.gov identifier: NCT01750957) Individuals will be treated with 2 doses (not specified) of RG7090 over 12 weeks
Fenobam (NPL2009)	Open-label, single-dose pilot study showed that 6 of 12 individuals with FXS had a >20% improvement in prepulse inhibition but no improvements in Continuous Performance Test[132]	Recruiting: phase 1, blinded, randomized, placebo-controlled, pharmacokinetic study of fenobam 50, 100, or 150 mg in healthy adult volunteers
$GABA_BR$ agonist		
Arbaclofen (STX209)	Phase 2 randomized, double-blind, placebo-controlled trial of 63 individuals with FXS. No improvement in ABC-irritability subscale (the primary end point); however, improvements on the VAS ratings of parent-nominated behaviors and ABC-social avoidance subscale were noted[133]	Study terminated: phase 2, open-label, efficacy and safety extension study in 45 children and adults with FXS (ClinicalTrials.gov identifier: NCT01013480) Study terminated: phase 3 open-label trial to evaluate efficacy, safety, and pharmacokinetics in 357 individuals with FXS aged 5–50 years (ClinicalTrials.gov identifier: NCT01555333) Two phase 3, double-blind, placebo-controlled trials for the treatment of social withdrawal in individuals with FXS Completed: adolescents and adults, aged 12–50 years (n = 125) (ClinicalTrials.gov identifier: NCT01282268) Completed: children, aged 5–11 years (n = 172) (ClinicalTrials.gov identifier: NCT01325220) Primary end point for both trials is the ABC-lethargy social withdrawal subscale
$GABA_AR$ agonist		
Ganaxolone	None	Recruiting: phase 2, double-blind, controlled trial in up to 60 children with FXS, aged 6–17 years, to assess safety, tolerability, and efficacy (ClinicalTrials.gov identifier: NCT01725152)
Acamprosate	Retrospective review of medical records for 3 individuals with FXS and autism receiving acamprosate for 16–28 weeks showed a global clinical benefit as rated on the CGI-Improvement scale score for all individuals[134] Open-label, uncontrolled study in 7 individuals with FXS and autism and 6 individuals with autism alone[135] Significant improvements from baseline in all outcome measures were observed (CGI-Irritability, CGI-Severity, ABC scales and VAS) 10 of 13 individuals were reported to be clinical responders	Recruiting: phase 2/3 double-blind, placebo-controlled, proof-of-concept study in 48 adolescents, aged 5–18 years (ClinicalTrials.gov identifier: NCT01911455) Completed: phase 3, open-label, uncontrolled efficacy study in individuals aged 5–17 years with FXS (ClinicalTrials.gov identifier: NCT01300923)

(continued)

Table 2 (continued). Therapies Targeting the Underlying Cause of Fragile X Syndrome (FXS) That Are Undergoing Clinical Trials

Agent	Clinical Evidence in FXS	Status of Planned or Ongoing Trials
Other signaling pathways		
Minocycline	Survey of 50 individuals who received minocycline for at least 2 weeks reported an improvement in language and behavior areas according to parents' feedback[136] An open-label, 8-week trial, in 20 individuals aged 13–32 years treated with minocycline 100–200 mg for 8 weeks reported significant improvements in ABC-C irritability subscale and VABS[137] Adverse events were generally mild A double-blind, placebo-controlled trial in 55 children and adolescents, aged 3.5–16 years, showed positive results in the CGI-Improvement scale score and in mood and anxiety problems as measured by a VAS[138]	None ongoing
Lithium	Open-label study in 15 individuals with FXS showed that 2 months of treatment with lithium significantly improved total ABC-C, VAS, CGI, VABS, and RBANS list learning scales[139] Lithium improved anxiety, tantrums, mood swings, and aggression; and caregiver ratings indicated improvements in hyperactivity and inappropriate speech	None planned
Melatonin	A 4-week, randomized, controlled, phase 2 trial of 12 children with autism and FXS showed significant improvements in mean sleep duration, mean sleep-onset latency, and mean sleep-onset time[140]	None planned
Donepezil	Open-label pilot study of 8 individuals with FXS, aged 14–44 years. Subjects demonstrated improvements in ABC total, irritability, and hyperactivity scores and contingency naming task scores (a measure of working memory and mental flexibility)[141]	Recruiting: phase 2 RCT of 50 individuals with FXS, aged 12–29 years, receiving donepezil 2.5–10 mg/d for 12 weeks (ClinicalTrials.gov identifier: NCT01120626)
Sertraline	Open-label study of 11 children with FXS. Sertraline improved receptive and expressive language development in comparison to controls[142]	Recruiting: phase 2, double crossover RCT of 72 children, aged 24–68 months, receiving sertraline 2.5–5 mg/d for 6 months (ClinicalTrials.gov identifier: NCT01474746)
Lovastatin	Open-label case reports (R. J. H., unpublished data, 2013)	Planned controlled trial
Memantine	Retrospective review of medical records for 6 individuals with FXS and repetitive developmental disorders showed no significant improvement on CGI-Irritability scales or other symptom-specific rating scales[143]	Recruiting: phase 2, double-blind, placebo-controlled, dose escalation (5–20 mg) study for symptoms of FXTAS in 180 individuals aged > 30 years (ClinicalTrials.gov identifier: NCT00584948)
Riluzole	Open-label study in 6 individuals with FXS showed no significant improvement in the CGI-Irritability subscale[144]	None planned
CX516	Phase 2, randomized, double-blind, placebo-controlled, 4-week trial in 49 individuals with FXS showed no significant improvement in cognitive and behavioral outcome measures compared with placebo[145]	None planned
Oxytocin	A double-blind placebo controlled study of 10 male adolescents (13–24 y) with FXS receiving a single dose of 24 or 48 IU of oxytocin or placebo, over 3 consecutive wk (1 wk apart). Eye contact was significantly improved with the 24-IU dose compared with placebo, and salivary cortisol levels were significantly reduced with the 48-IU dose compared with placebo[150]	None planned

Abbreviations: ABC = Aberrant Behavior Checklist, ABC-C = Aberrant Behavior Checklist-Community, CGI = Clinical Global Impressions, FXS = fragile X syndrome, FXTAS = fragile-X-associated tremor/ataxia syndrome, $GABA_AR$ = γ-aminobutyric acid-A receptor, $GABA_BR$ = γ-aminobutyric acid-B receptor, IU = international unit, LTD = long-term depression, mGluR5 = metabotropic glutamate receptor 5, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, RBS-R = Repetitive Behavior Scale-Revised, RCT = randomized controlled trial, SRS = Social Responsiveness Scale, VABS = visual analog scale of behavior, VAS = visual analog scale.