Submission to Senate Foreign Affairs Defence and Trade References Committee

Inquiry into the ADF use of Mefloquine and Tafenoquine

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As I have contributed to the Joint Health Command ADF submission to the committee, this personal submission only addresses the generic assertions by those veterans who have called for the inquiry.

Since this submission was written the US Food and Drug Administration has approved tafenoquine (20 Jul 2018) for the treatment of relapsing malaria.

It is a personal submission and does not necessarily reflect the views of the ADF.

Response to generic claims of harm by veterans participating in antimalarial drug trials

There is a group of ADF veterans who feel that they have suffered adverse events, particularly neuropsychiatric symptoms, which were caused by participating in antimalarial drug trials in 2000-2002 particularly in East Timor. The claims can be summarized generically as soldiers who participated in antimalarial drug trials were not informed of potential of adverse events as required by ethical conduct of human investigations, were not true volunteers due to command pressure to participate, had a variety of symptoms while taking the medications in East Timor and several years after return to Australia developed latent "chemically induced brain injury" whose many neuropsychiatric symptoms resemble PTSD. The first two assertions listed have already been answered by an ADF Inspector General's report and the third was documented in great detail by clinical investigation records at the time. As the Therapeutic Goods Administration (TGA) is the statutory body in Australia responsible for drug efficacy and safety and tafenoquine is currently being considered for registration, it seems best if the TGA is allowed to do their analyses of the large number of individual clinical records and render an unbiased opinion when they feel ready to do so.

This leaves the issue of chemically induced brain injury which has already been considered by the Repatriation Medical Authority which decided not to make a Statement of Principles regarding chemically acquired brain injury due to antimalarial drugs 18 Aug 2017. The assertions by those claiming harm can be summarized as some antimalarial drugs are neurotoxic even when given in ordinary treatment and prophylaxis dosages and many veterans who took these medications developed serious adverse events years afterwards. As with all arguments of causation, there are elements of truth contained within the assertions regarding the toxicity of antimalarial drugs. However, the facts do not support the version of events put forward by some veterans which has symptoms developing years after drug administration and thus causing current neuropsychiatric symptoms.

Post military deployment neuropsychiatric events have been commonly noted for over a century. After each war, a new nomenclature was developed to try to describe the multi-faceted presentations and symptoms seen in a new generation of soldiers. Soldiers are a direct reflection of the society from which they are recruited. Armed combat is probably the most stressful human condition imaginable, but soldiers also experience high rates of family separations, martial breakdown as well as a multitude of other social stressors in non-war like situations which contribute to and may cause neuropsychiatric symptoms. Trying to assign any single cause to various post-military, veteran's illnesses does not accurately reflect the many potential contributors to a soldier's mental and physical health.

In any human characteristic that is subject to accurate measurement, the population usually falls along a Poisson distribution, that is a bell curve with most in the big middle and a few at the two extreme ends. Those at the high end feel no need to explain their success and those in the middle know that is where they expected to be located with the majority. Those people at the low end crave a narrative that explains why they are the unfortunate few be it due to heredity, chance or some unrelated event. The explanatory narrative once formed, becomes an article of faith and any attempt to change it is resisted strongly regardless of data to the contrary. The tragedy is when the narrative locks persons needing care into a dysfunctional cycle of recrimination reinforcing an illness pattern confirming the narrative. Such a cycle blocks a person's ability to take advantage of any positive therapeutic interventions.

These assertions are therefore reviewed below in this context.

Assertion 1: Antimalarial drugs cause serious neuropsychiatric effects which may become apparent years later

As with all drugs, antimalarial drugs are known to have adverse events some of which include neuropsychiatric symptoms. Over time, improved medications have resulted in fewer adverse events, but the medications used in the first part of the 20th century such as quinine, quinacrine and pamaquine all had serious adverse neuropsychiatric effects in a minority of persons. Quinine is a short acting medication which usually cannot be tolerated for long due to "cinchonism" with tinnitus and other dysphoric symptoms. Quinacrine (atabrine) was used by millions of soldiers during the Second World War especially in New Guinea and SE Asia. Seizures and psychosis was described in about 2 per 1000 soldiers receiving quinacrine especially in higher doses or when injected. These symptoms developed within days of receiving the medication and in the vast majority of cases resolved within a month of stopping the drug. In a few cases quinacrine was thought to have possibly exacerbated a previously undiagnosed and pre-existing neuropsychiatric condition such as schizophrenia. The veterans of the Second World War have nearly passed from scene, but there has been no solid evidence that medical conditions in later life were caused by quinacrine taken while soldiers. Pamaquine, the first 8-aminoquinoline drug (similar to primaquine and tafenoquine) was known to be toxic in relatively small doses but most adverse events were due to GI upset or hemolysis in sensitive persons with a genetic deficiency of glucose-6-phosphate dehydrogenase (G6PD). Neuropsychiatric adverse events were not typical of the problems experienced with pamaquine which was abandoned by the US Army due to its hemolytic potential.

Mefloquine is known to have serious neuropsychiatric effects that can include seizures and psychosis. Treatment doses (≥ 3x prophylaxis) are much more prone to severe adverse effects (estimated 1:1000) but it is difficult to delineate the true cause when a person is suffering simultaneous malaria symptoms. Estimates of the Severe Adverse Effect (SAE) rates from chemoprophylaxis are difficult to evaluate due to the uncertainty in how many travelers took the medication but German studies estimated 1:8000 had neuropsychiatric SAEs. The drug effect disappears as the drug is cleared from the body over several weeks. Tens of millions of doses of mefloquine have been and continue to be successfully used as malaria treatment despite it having been largely abandoned for chemoprophylaxis in Western travelers. If mefloquine has long-term effects after its discontinuation, it is thought to be as a stressor that reveals a pre-existing condition particularly depression. Although claimed as a cause of suicides, drug tests of completed suicides in the US Army have not found such an association. A major survey of Bougainville and East Timor ADF veterans was conducted in 2008 by the Centre for Military and Veterans Health incorporating questions on antimalarial use and self-reported health status. Few veterans reported mefloquine use such that no conclusions about the drug were possible; only 3% of the responding ADF veterans deployed to Bougainville or East Timor claimed to be in poor health.

Primaquine is the drug that replaced pamaquine after an emergency program caused by the Korean War sending thousands of US Army veterans back into the USA with relapsing malaria and the potential to re-start malaria transmission in the Southern USA. Doses several times higher than the usual 15-30 mg have not resulted in any direct association with neuropsychiatric events. Tafenoquine has been tested in a few thousand persons as part of its development for the treatment of relapsing malaria as well as chemoprophylaxis. In controlled trials with placebo or an active comparator such as mefloquine, the neuropsychiatric symptoms (most commonly headache) experienced were not significantly different between groups.

Assertion 2: Antimalarial drugs are associated with and have enabled many suicides in ADF veterans

Suicide is an increasing cause of death in Western countries driven by a variety of societal factors including advancing life-expectancies, increasing rates of mental depression, increased use of drugs such as opiates, as well as increasing societal acceptance of suicide as a rational choice when very old or in great pain. Suicides in the ADF have been very carefully studied and are at significantly lower rates than the general population likely due to the selection process for military service which produces a "healthy soldier effect". One exception is veterans with very short ADF service likely reflecting recruits who were unsuccessful in completing initial soldier training or were discharged as unsuitable within a few months. Few of any such soldiers / veterans would have been deployed overseas or received antimalarial drugs.

Antimalarial drugs are associated with suicides in the sense that intentional over dose with chloroquine is one of the most common drugs used globally to kill oneself. Chloroquine has been popularly recommended as an easy means to death and remains the most common drug used for suicide attempts in many European and tropical countries such as Papua New Guinea. The therapeutic margin (difference between efficacious and lethal dosages) of chloroquine is narrow. Some children have died after twice an ordinary dose; adults usually receive 1.5 gm of drug for malaria treatment whereas 5 gm is considered as usually lethal without extraordinary medical interventions. This is despite chloroquine's reputation as a safe drug. It seems likely that lethality and reputation are mis-matched with chloroquine as death occurs from cardiac dysrhythmia, a death that leaves no visible traces unlike primaquine that causes remarkable blackwater urine after hemolysis from glucose-6-phosphate dehydrogenase deficiency (G6PD). As recently as the 1990s, the numbers of civilian malaria deaths in Australia were sometimes no more than those dying of intentional or unintentional chloroquine over doses. The TGA action to eliminate chloroquine from the formulary (hydroxy-chloroquine is still available for rheumatological indications) directly relates to the lethal potential of chloroquine when mis-used.

The question of suicides in the veteran population and its possible associations is more difficult to address for several reasons; veteran status is not counted on a population basis, suicide remains under counted due to residual societal proscriptions against killing oneself and the difficulty many coroners have in making a determination of death when it occurs without previous medical supervision. If mefloquine has any impact on suicide in the ADF and veteran's community it would have to be because of effect generated years after its use as very little mefloquine has been used in the recent past in Australia (<12,000 scripts in 2016) generally and the ADF (2 in 2017) specifically. Although temporary neuropsychiatric adverse events are noted when using mefloquine, the assertion that it causes suicidal behavior long after the drug has left the body is both pharmacologically implausible and in direct contradiction to the vast experience in countries where mefloquine continues to be used for malaria treatment in many hundreds of thousands of people.

Assertion 3: Antimalarial drugs are toxic to laboratory animals and toxicity in animals means the drug is toxic to man

Determination of toxicity in laboratory animals is a required step in drug development to give some estimate of the drug's possible adverse events when used in humans. At least two species of animal (e.g. rat and dog) are used with the very expensive primate models (rhesus monkeys) considered the best reflection of what is likely to happen in man. The use of different species is due to the common observation that toxicity seen in one animal will not be seen in a different species. This intrinsic variability makes even standard toxicology assays part science and part art based on experience with similar drugs when used in man. Drug dosages in animal toxicity studies are always used at several times the dosage expected for use in humans to ascertain what might occur in exceptional people. Toxicity in animals is worrisome but not always reflected in man.

Two examples in terms of antimalarial drugs are instructive. Chloroquine is widely regarded as a safe drug on the basis of its use in literally a billion people. Yet a single tablet of chloroquine (300 mg) will kill a dog and was the reason the German discoverers of the drug did not pursue its development. It was only when the US Army found records of chloroquine's use by French scientists in Algerian patients that interest in its potential drove chloroquine's development which was only completed after the Second World War ended.

Chloroquine was the basis of all antimalarial treatment for over a generation from 1950. Now artemisinins are the standard treatment drug. Derived from traditional Chinese Medicine by a large multi-faceted Chinese Army unit in the 1960s because of the Vietnam War, artemisinin (e.g. artesunate, artemether) compounds have become the basis of modern malaria chemotherapy. Artemisinins were slow to be introduced into the West due to the completely different approach to drug development. Chinese scientists started from what was being used in man and then tried to isolate the active ingredient of complex organic mixtures such as teas. Western scientists used the classical approach of starting with a large number of defined chemical entities and then testing them in the laboratory to see which might give the desired effect. This disconnect was observed when World Health Organization (WHO) experts described the marked neurotoxicity of artemisinin in laboratory animals and asked their Chinese counterparts about it. The Chinese certainly knew of the toxicity in monkeys but largely ignored it as the compound was already being used in man including even pregnant women, an unthinkable occurrence to the non-Chinese experts. Classical drug development would have abandoned the drug long before it reached human testing due to its distinct neurotoxicity. Even after these observations were known, it was difficult for the groups to reconcile the use of such a drug in a globally sanctioned manner by the WHO which delayed the introduction of artemisinin combination therapies.

The clinical and public health usefulness of artemisinin compounds used in over a billion patients speaks for itself. In 2015 Professor Tu You You was awarded a half share of the Nobel Prize in Medicine and Physiology in recognition of her key role in finding that the active ingredient of artemisinin was in an organic extract of a common type of bush (artemisia) used in Chinese herbal medicine. For the two most common antimalarial drugs ever used, there was no relationship between animal toxicity and the drug's eventual clinical usefulness in man. One cannot state that animal toxicity, especially when used in very high concentrations, is directly indicative of a human effect; it is only a possibility which needs to be closely monitored during investigational testing.

Assertion 4: Investigators within the ADF will benefit financially from tafenoquine

Antimalarial drugs rarely make any profit. Drugs to keep poor people from dying are not nearly as attractive financially as drugs to keep rich people well. The military has been at the center of anti-malarial development through the 20th century simply because there was no commercial motivation to make antimalarial drugs once malaria was eliminated from the USA and Europe by the 1950s. Even when organizations such as the US Army sponsor a drug's development with many millions of dollars, the supply of the drug is still put out to contract to a commercial organization like any other product bought by the military. Until recently US government laboratories could not participate in commercial drug development as government research was not patented. Regardless both mefloquine and tafenoquine were synthesized in the 1980s and any commercial patent protection has long since expired. Anyone can make these antimalarial drugs so they are largely made by the lowest cost producers in India and China. Although quality drugs are made in both countries, so are many counterfeit and fraudulent medications that kill when poor families buy these lower cost fake medicines. The market for antimalarial drugs is vast through the developing world, but problematic and rarely profitable.

Drugs for public health use in the developing world do not have a profit driven procurement procedure. Charitable organizations such as the Bill and Melinda Gates Foundation have financed much of the development of tafenoquine (and many other drugs for the developing world) through the public private partnership known as Medicines for Malaria Venture (mmv.org). This not-for-profit organization based in Switzerland has for the last 25y manages a global portfolio of antimalarial drugs from discovery through to field access. Prices for a single adult malaria treatment have to be kept below about $1 US in order to make them available to the people who need them. Some of these drugs are procured as subsidized medications through pre-qualification programs of the World Health Organization financed by various donor organizations. The Australian Department of Foreign Affairs and Trade is an active participant in the regional commitment to eliminate malaria from the Asia Pacific by 2030. This has included increased support for MMV with some of the funding specifically designated for tafenoquine.

Pharmaceutical firms are able to claim a "voucher" from the US Food and Drug Administration (FDA) when they register a product for a rare or neglected disease which is a way that the US Government indirectly subsidizes work on otherwise unprofitable conditions. As the definition is based on the number of US citizens developing the disease, malaria is considered a neglected disease despite it being a very common infection in the tropics. US FDA vouchers give the pharmaceutical firm involved the opportunity to speed up the registration process for their next drug by six months. When used for a very profitable drug such as ones for erectile dysfunction, this can translate into millions of dollars. On the other hand, one such voucher that the international pharmaceutical company GSK applied to their investigational drug for gout ended up with zero value when the drug failed late stage clinical trials. Vouchers can be auctioned to other companies but the price obtained depends on the market and the multiple vouchers issued recently have depressed any potential auction price. GSK has recently (July 2018) received a voucher for the registration of tafenoquine by the US FDA for treatment of relapsing malaria. Whatever money is eventually received for the voucher will largely be applied to the currently unfunded costs of introducing tafenoquine into malaria endemic countries such as Indonesia and Brazil. The $100s of millions both GSK and the US Army spent on the development of tafenoquine over > 20y will never be recovered. The US FDA voucher is only a small offset against the cost of drug development.

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